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# SEMINAR TOPICS

CHEMISTRY 435

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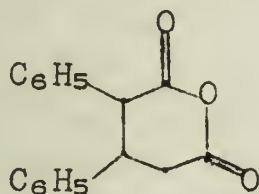
FIVE- vs. SIX-MEMBERED RING FORMATION IN THE ACID CATALYZED  
CYCLIZATION OF ARYL SUBSTITUTED CARBOXYLIC ACIDS

Reported by D. Lednicer

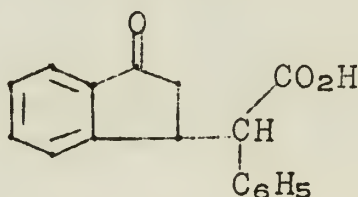
September 15, 1958

INTRODUCTION.

It is well known, largely as a result of the work of von Braun and collaborators (1,2) that a six-membered ring will generally be formed in preference to a five-membered one in the Friedel-Crafts cyclization of aryl substituted acids. For example, the treatment of the acid chloride of either 2-benzyl-4-phenylbutyric acid or that of 2-benzylsuccinic acid with aluminum chloride affords exclusively the tetralones (3). Recently a deviation from this rule was reported by Badger (4) who showed that the anhydride of 2,3-diphenylglutaric acid under cyclizing conditions affords the indanone II in good yield.



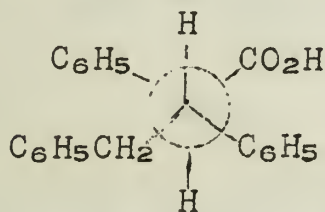
I



II

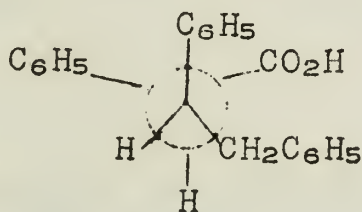
THEORETICAL CONSIDERATIONS.

An examination of molecular models of some highly substituted acids existing as diastereomers suggests that in some cases at least the formation of a five-membered ring may be favored over the more usual six-membered ring formation for reasons of conformational stability. In the case of 2,3,4-triphenylbutyric acid, for example, the threo isomer would be expected to lead to a tetralone since the carboxyl group has easy access to the required phenyl ring in the preferred rotamer (III). In the case of the erythro isomer on the other hand, the carboxyl group of the preferred rotamer (IV) can attack only that phenyl ring which would lead to an indanone; to form a tetralone this molecule must assume the highly crowded conformation shown in V.

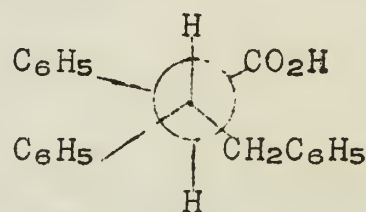


IV

erythro



V



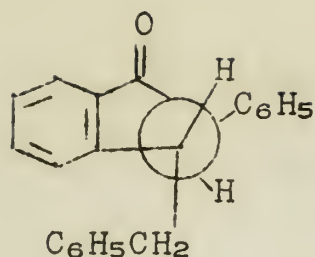
III

threo

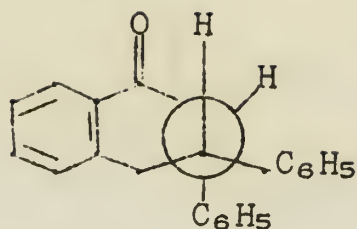
If the transition state leading to the cyclic product more closely resembles the product than it does the starting material, the same results may be expected since IV will lead to the indanone VI which is less overcrowded than is the tetralone VII, which would result from the cyclization of the rotamer V. The latter ketone contains the two phenyl rings in the syn relation.







VI



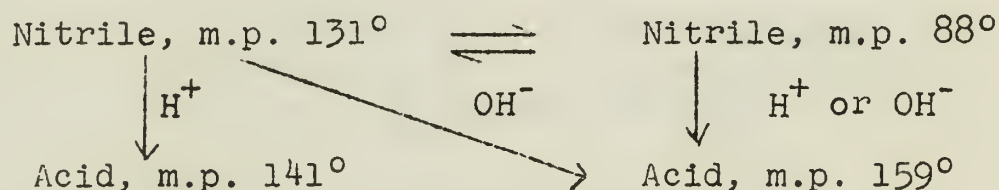
VII

Similar considerations apply to the cyclizations of 3,4-diphenylvaleric acid and 2,3-diphenylglutaric acid. These are discussed in greater detail below.

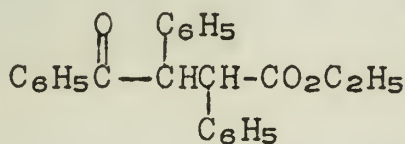
### 2,3,4-TRIPHENYLBUTYRIC ACIDS (11).

The known isomer of 2,3,4-triphenylbutyronitrile (5,6) was equilibrated with a catalytic amount of potassium ethoxide in ethanol solution. Fractional crystallization of the product afforded the known nitrile, m.p. 131°, and its isomer, m.p. 88°, in roughly equal amounts. Hydrolysis of each nitrile under acidic conditions afforded the corresponding acid. When basic hydrolysis was employed each of the nitriles led to the higher melting acid (Scheme A).

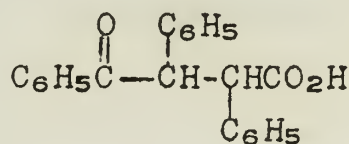
#### Scheme A



These results indicate that the high melting acid is the more stable of the two. Support for this comes from the observation of Crawford that alkaline hydrolysis of VIII afforded predominantly that isomer of IX which on reduction gave the 159° m.p. isomer of the butyric acid (7).



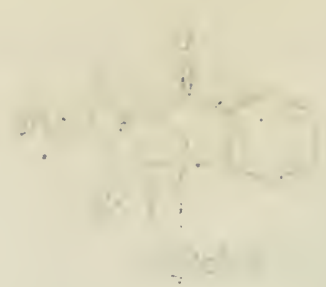
VIII



IX

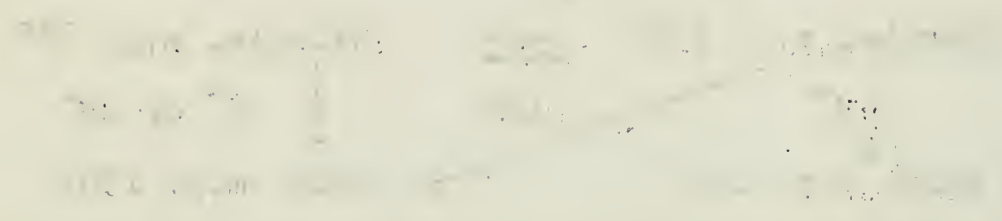
Molecular models suggest that the threo isomer has the greater stability since in the least crowded conformation the largest group (benzyl) is placed next to the smallest group (carboxyl) as in III. The acid of m.p. 159° would thus be the threo isomer.

Treatment of the erythro acid with hydrogen fluoride afforded a good yield of neutral material. The presence of bands at both 1718 and 1686 cm.<sup>-1</sup> suggested that both the known tetralone X and the indanone XI were present. Due to the very similar solubility characteristics of these two compounds the mixture was separated manually.

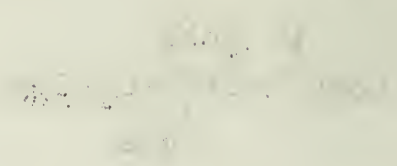


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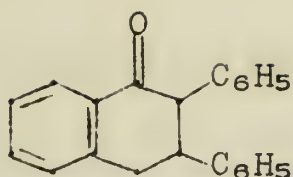
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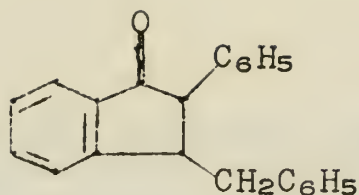
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X

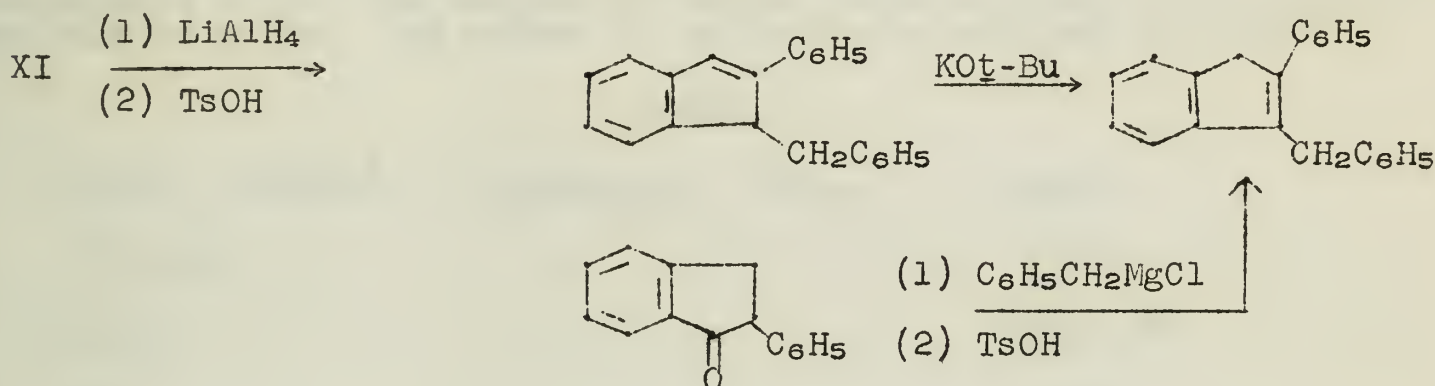


XI

The infrared band at  $1686\text{ cm.}^{-1}$  was shown to be due to the known tetralone. The purified material which showed the  $1718\text{ cm.}^{-1}$  band was proven not to be the diastereomer of X by reduction followed by dehydration. Since each of the ketones yielded a different olefin, their carbon skeletons must also be different.

The presence of the five-membered ring in the cyclization product XI was demonstrated as shown in Scheme B.

Scheme B



Each isomer of the acid was treated with hydrogen fluoride. Its corresponding acid chloride was subjected to cyclization with stannic chloride in refluxing benzene. The proportion of the five- and six-membered ketones formed was estimated from the relative intensities of the infrared bands in the spectrum of the total neutral material isolated from the cyclization reactions. A calibration curve was prepared from mixtures of X and XI of known concentrations. Table I shows the results.

Table I

<u>Starting Acid</u>	<u>Cyclizing Agent</u>	<u>Relative Proportion of:</u>	
		<u>Tetralone X</u>	<u>Indanone XI</u>
erythro	HF	1	2
threo	HF	3	1
erythro	$\text{SnCl}_4$	6	1
threo	$\text{SnCl}_4$	20	<1

It thus appears that the relative stereochemistry of cyclization does exert an influence on the path of the ring closure reaction. The effect is most pronounced in liquid hydrogen fluoride. The great discriminating power of this reagent in another connection has been recently described by Denney (8), who observed an isotope effect with this reagent far greater than that of other acids.

10/10/50

10

10/10/50

10/10/50

The following information was obtained from the records of the Department of the Interior, Bureau of Land Management, regarding the land owned by the United States in the State of California.

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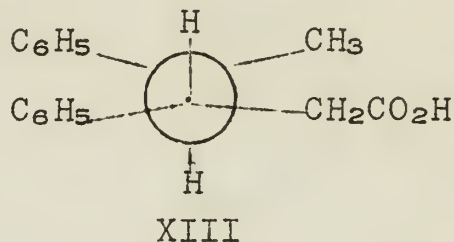
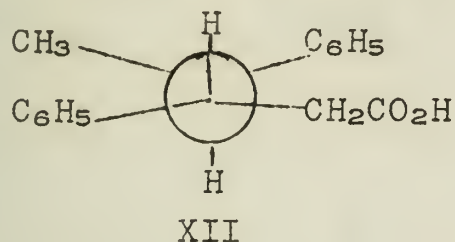
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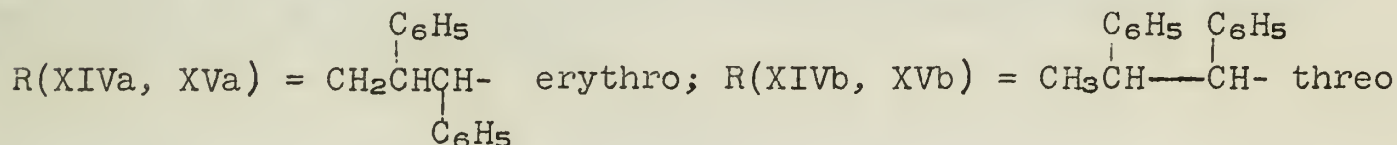
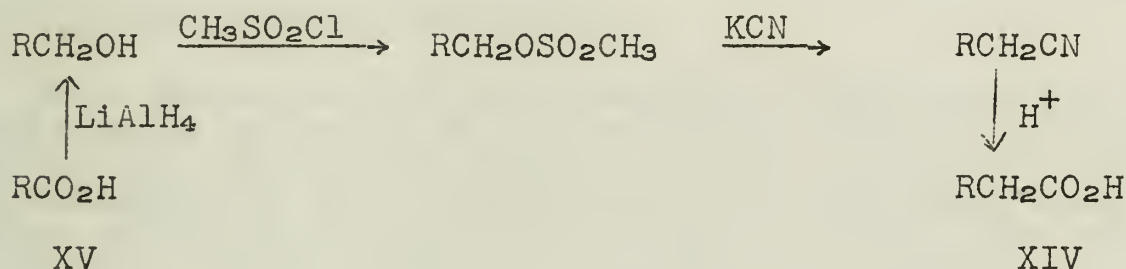
### 3,4-DIPHENYLVALERIC ACIDS (12).

Models of the two diastereomers of this compound suggest that here too a divergence may be found in the route of the cyclization. Thus the projection formulas suggest that the erythro isomer (XII) would favor the formation of a tetralone and the threo isomer (XIII) the formation of an indanone.



Since the configuration of the 2,3-diphenylbutyric acids had been established (9) it was decided to employ these to prepare the homologous valeric acids. The method of synthesis is outlined in Scheme C.

#### Scheme C



That the valeric acids XIVa and XIVb were clearly different was taken as evidence for the fact that the stereochemical identity of the carbon skeleton was unaffected by these transformations.

The cyclization of the higher melting (erythro) acid in sulfuric acid has been reported previously to give a tetralone (10). The same result was obtained in the present study using hydrogen fluoride. The crude product exhibited a band in the infrared at  $1681 \text{ cm}^{-1}$  and only a very small shoulder at higher frequency. Similar treatment of the threo acid gave a crude product which also showed a strong band at  $1681 \text{ cm}^{-1}$ ; however, this was accompanied by a sizeable shoulder at  $1709 \text{ cm}^{-1}$ . From this the estimate was made that indanone was present to the extent of about 10%.

Purification of the cyclization product of XIVb gave a ketone which was different from that obtained from the erythro isomer of the acid. Cyclization of the latter should lead to a trans tetralone while the threo acid should give the cis ketone. It was shown that the ketones were diastereomers by converting both to the same substituted naphthalene (Scheme D).



For a full and complete description of the new method of treatment of the various forms of syphilis, see the special article on this subject in the issue of the 15th of April, 1919, page 1000.



The following table shows the results of the treatment of the various forms of syphilis, as given in the special article on this subject in the issue of the 15th of April, 1919, page 1000.

TREATMENT OF THE VARIOUS FORMS OF SYPHILIS	
Form of Syphilis	Results of Treatment
Primary	100%
Secondary	100%
Tertiary	100%
Gonorrhea	100%
Chlamydia	100%
Trichomonas	100%
Yeast	100%
Parasites	100%
Bacteria	100%
Fungi	100%
Viruses	100%
Protozoa	100%
Helminths	100%
Arthropods	100%
Molluscs	100%
Echinoderms	100%
Cnidarians	100%
Ctenophores	100%
Tunicates	100%
Chordates	100%
Mammals	100%
Birds	100%
Reptiles	100%
Amphibians	100%
Fish	100%
Invertebrates	100%

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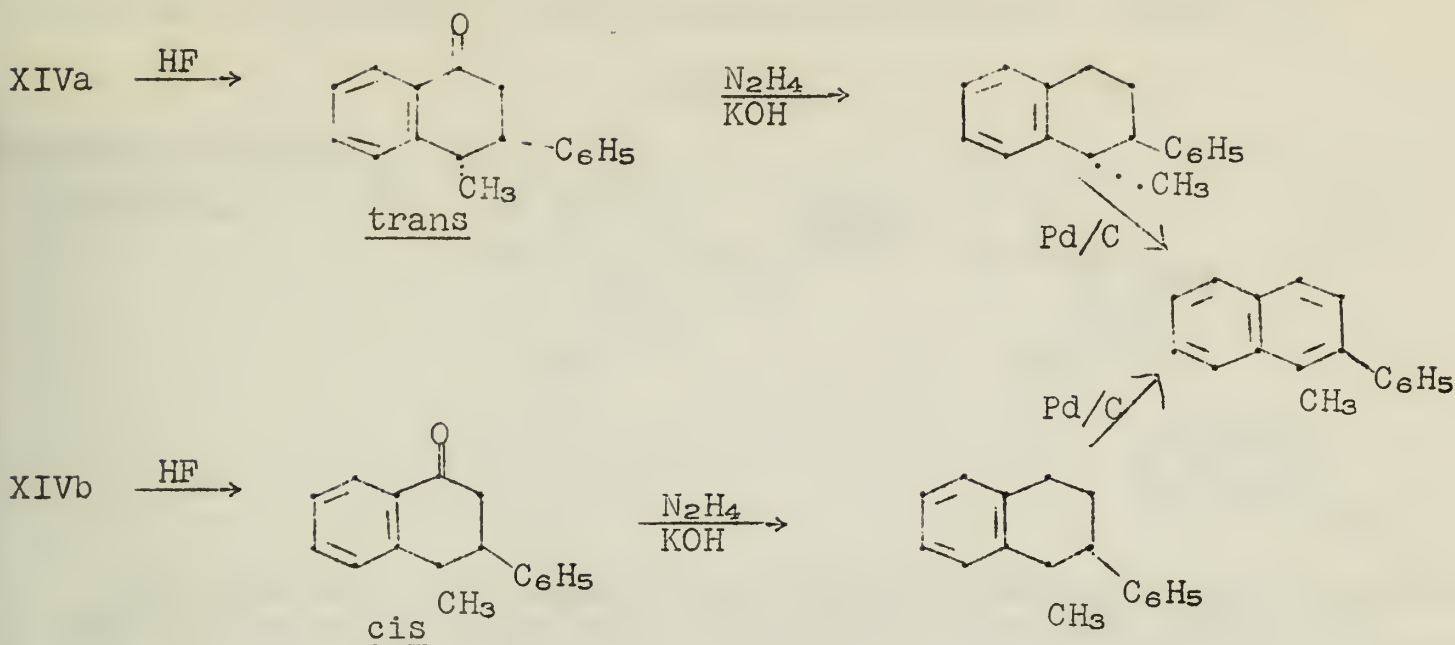
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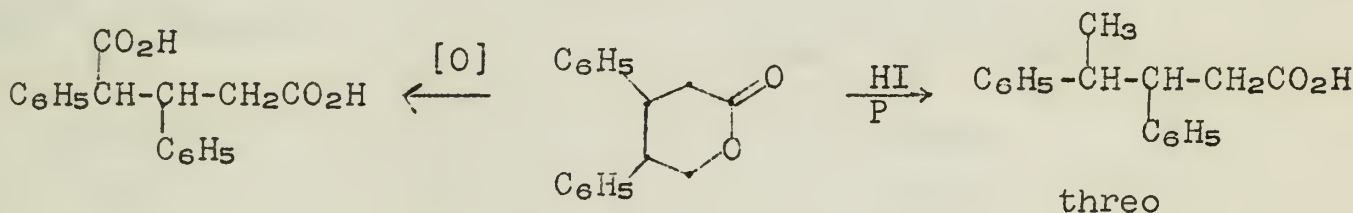
Scheme D



2,3-DIPHENYLGLUTARIC ACIDS (12).

Both isomers of this acid are known, the one of m.p. 208-210° being readily converted to that melting at 231-232°. On the basis of the rotations of the four optical isomers of the acid the former has been assigned the threo configuration and the higher melting acid the erythro configuration (13). In earlier work (14) the low melting acid was related to the valeric acid as shown in Scheme E. Since the valeric acid obtained in this manner has now been identified as the threo isomer the original assignment of configuration has in effect been confirmed by chemical means.

Scheme E



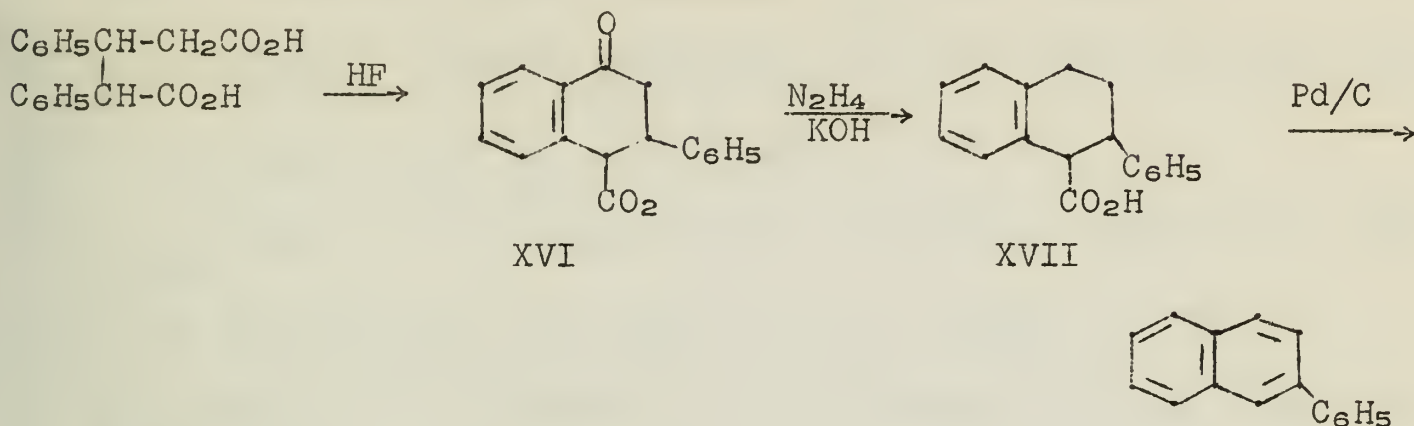
It has been demonstrated that the anhydride (I) employed for the cyclization by Badger also has the threo configuration (12,13).

Treatment of the high melting erythro acid with liquid hydrogen fluoride afforded a good yield of acidic material which showed absorption at both 1718 and 1681 cm.<sup>-1</sup>. Repeated crystallization was necessary to obtain the pure keto acid, m.p. 152-154° in 20% yield. This compound strongly depressed the m.p. (153-155°) of the known indanone II, which showed absorption at 1718 cm.<sup>-1</sup> only. Since the pure cyclization product still exhibited the same carbonyl bands as the crude product, a tetralone was indicated. Reduction of the keto acid XVI gave a good yield of an acid XVII which showed a band in the infrared at 1718 cm.<sup>-1</sup> only, indicating that the ketone is indeed a six-membered



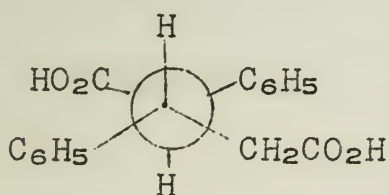
one. By way of final proof of the presence of the six-membered ring, XVII underwent dehydrogenation and decarboxylation on heating with palladium on charcoal to yield 2-phenylnaphthalene, (Scheme F).

Scheme F



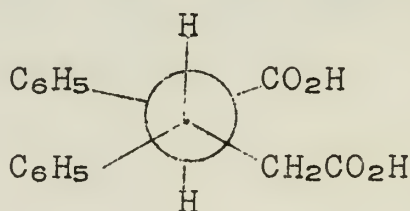
The threo acid on treatment with liquid hydrogen fluoride yielded a complex mixture of acids from which the authors were unable to isolate any pure compounds. The composition of this mixture could not be estimated since, as is shown above, the band at  $1718\text{ cm}^{-1}$  is common to the indanone carbonyl group and the carboxyl group.

Thus, no conclusion is warranted concerning the stereochemistry of the cyclization of the ring closure of the two diphenylglutaric acids. It is worth noting, however, that the erythro isomer is indeed that one which on steric grounds might be expected to form a six-membered ring. In the preferred conformation of that acid the carboxyl group is in a favorable position to form a tetralone (XVII) while the threo acid in the preferred conformation (XIX) favors an indanone.



erythro

XVII



threo

XIX





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# CONJUGATED EXOCYCLIC DIENES

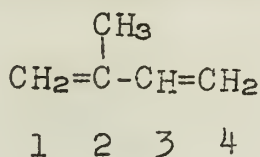
Reported by D. Longone

September 18, 1958

(A) 1,2-Dimethylene-cyclobutane, -cyclopentane and -cyclohexane.

The dependence of polymer properties on polymer structure is historically exemplified in the polyisoprenoid isomers gutta percha and hevea. The difference in properties of these two materials at room temperature is very striking. Hevea, or natural rubber, possesses the familiar elastomeric properties even at very low temperatures, while gutta percha is a hard, horny, non-elastomeric material which only softens when heated to about 50°.

Although it was known as early as 1904 (1) that both hevea and gutta percha were poly-1,4-isoprenes, it was not until the application of X-ray methods that the 2,3-double bond configuration in both polymers was elucidated. Hevea was shown to be cis-polyisoprene (2) while the isomeric gutta percha possessed the trans configuration (3). This fact led to the extreme assumption that a good elastomer could be obtained from almost any all-cis polydiene. A logical approach to the determination of the effect on polymer properties of cis and trans isomerism in isomeric poly-1,4-butadienes would be the synthesis and study of a series of such all-cis and all-trans polymers. However, until the very recent discovery of heterogeneous stereospecific catalysts it has been impossible to polymerize dienes to exclusively all-cis or all-trans structures. The use of either free radical, anionic or cationic initiators has always led to a mixture of structural units. For example, the free radical initiated polymerization of the symmetric diene, butadiene, yields a product which contains 18-22% 1,2-units, with the remainder a mixture of trans-1,4 and cis-1,4-units (4). The proportion of 1,2-units is relatively independent of temperature, while the ratio of trans-1,4 to cis-1,4-units decreases with an increase in polymerization temperature. In the case of an unsymmetrical diene such as isoprene, the product is even more complex.



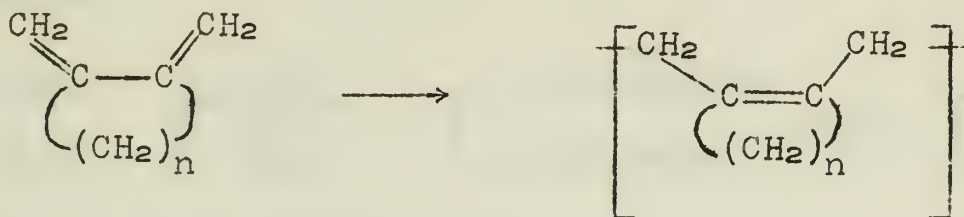
In addition to 1,4- and 1,2-units, 3,4-units can occur; moreover, units formed by 1,2-addition (also 3,4-addition in the case of unsymmetrical dienes) result in the formation of an asymmetric carbon atom which will occur essentially in a random sequence of d and l forms. Further heterogeneity results in the relationship of adjacent structural units. That is, in asymmetric dienes successive 1,4-units may not occur entirely in the more usual head-to-tail sequence. The fact that polyisoprene prepared at low temperatures will not crystallize on stretching or cooling as will low temperature polybutadiene may be explained by the occurrence of considerable head-to-head and tail-to-tail sequences of the 1,4-units in the former (5).

It is evident then that in the past it has not been possible to synthesize structurally pure diene polymers which would allow a fundamental study of gross polymer properties as related to polymer structure.



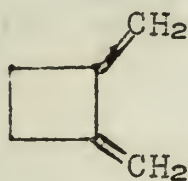


In 1950, several years before the advent of stereospecific catalysis, a general program utilizing a unique approach to the synthesis of geometrically homogeneous poly-1,4-dienes was initiated at Cornell University under the direction of Dr. A.T. Blomquist. In the work described here, dialkylbutadienes in which the 2- and 3-positions are part of a carbocyclic ring were of interest. In such conjugated exocyclic dienes where the ring is small ( $n \leq 5$ ), 1,4-polymerization must yield entirely cis-1,4-units due to the steric requirements of the ring.

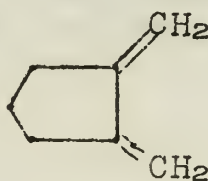


If the ring is unsubstituted the monomer is symmetrical and only one stereoisomeric 1,2-unit is possible. Furthermore, molecular models show unfavorable steric interactions resulting from 1,2-units with rings as pendant groups. The polymerization of such dienes should then afford polymers of high structural regularity similar in chain configuration to natural rubber.

The first two dienes investigated were 1,2-dimethylenecyclobutane (6) (I) and 1,2-dimethylenecyclopentane (7) (II).

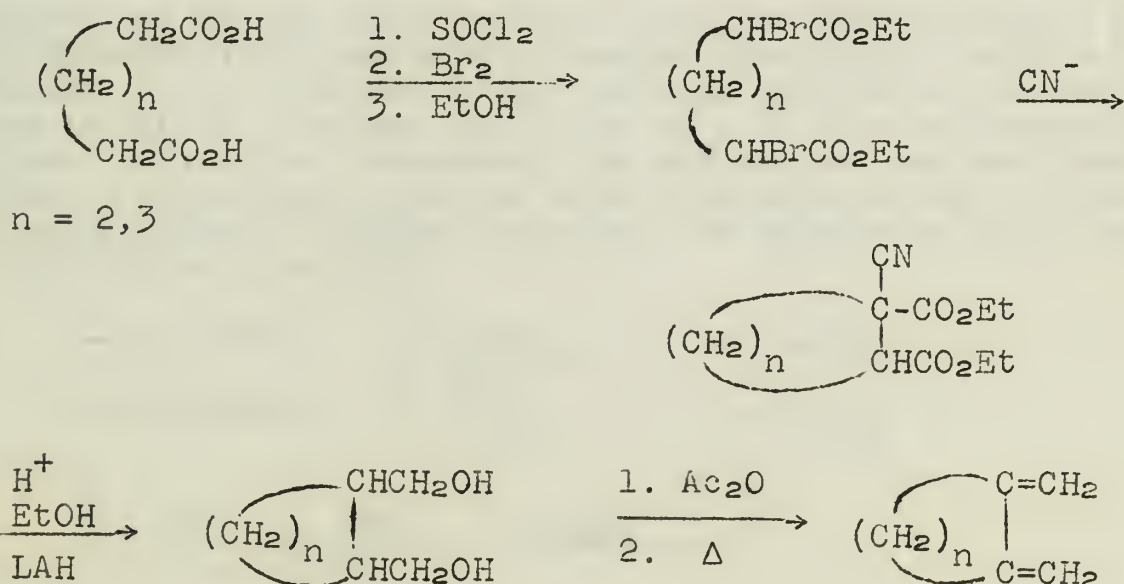


I



II

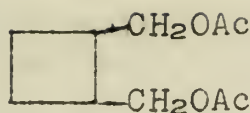
The proposed synthetic route to these dienes is outlined below:



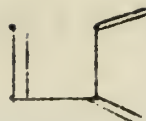
When 1,2-bis-(acetoxymethyl)-cyclobutane (III) was pyrolyzed at  $485^\circ$  none of the expected diene was obtained. The only product isolated was 2-vinyl-1,3-butadiene (6) (IV).





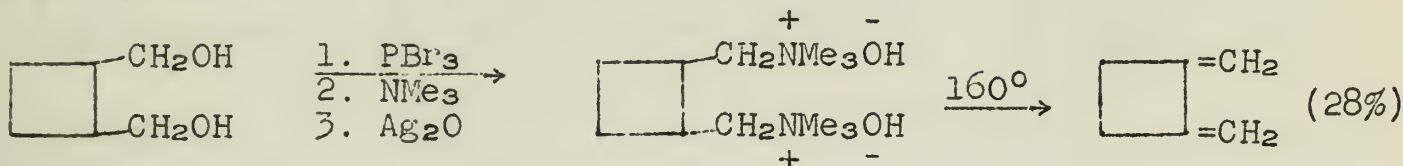


III



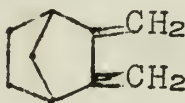
IV

The desired product was, however, obtained by the less drastic Hofmann pyrolytic method.



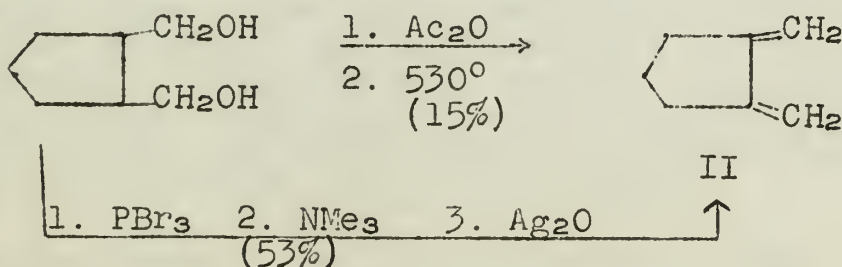
The product showed two principal absorption maxima in the ultraviolet:  $\lambda$  237 m $\mu$ , log  $\epsilon$  3.99 and  $\lambda$  246 m $\mu$ , log  $\epsilon$  4.01.

During the progress of the work on dimethylenecyclopentane (II), the synthesis by pyrolysis of 1,2-bis-(acetoxymethyl)-cyclopentane was reported by Bailey and Sorenson (8). However, some of the properties reported for the product, notably the ultraviolet absorption spectrum, were at variance with what might be expected for a homolog of 1,2-dimethylenecyclobutane (I). It was reported that II exhibited no maxima in the ultraviolet region above 220 m $\mu$ . However, the spectrum of a closely related model compound, 2,3-dimethylenebicyclo[2.2.1]heptane (V), shows  $\lambda_{\max}$  249 m $\mu$ , log  $\epsilon$  4.06 and  $\lambda_{\max}$  240 m $\mu$ , log  $\epsilon$  3.99 (9).



V

Inasmuch as it had been observed earlier that pyrolysis of 1,2-bis-(acetoxymethyl)-cyclobutane proceeded abnormally to form 2-vinyl-1,3-butadiene it was suspected that perhaps abnormal products were also being obtained from the pyrolysis of 1,2-bis-(acetoxymethyl)-cyclopentane. In order to compare the methods of acetate pyrolysis and Hofmann elimination, with the object of determining which is better for obtaining dienes of highest purity, the synthesis of II was continued applying both methods.

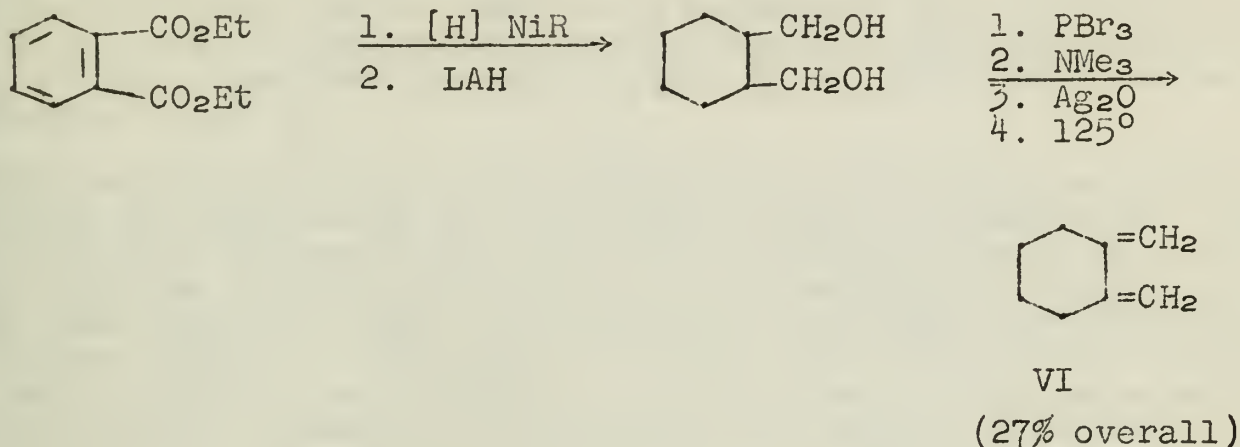


It was found that the Hofmann method afforded a product of greater purity and in higher yield. It also gave a single product, whereas the acetate pyrolysis gave a mixture of products which had to be carefully fractionated to yield pure diene. Purified II prepared by both



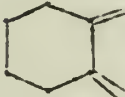


methods had a maximum absorption at  $\lambda$  248 m $\mu$ ,  $\log \epsilon$  4.02, in good agreement with the model V.

In order to complete the series of symmetrical conjugated exocyclic dienes for polymerization studies, 1,2-dimethylenecyclohexane (VI) was prepared using the Hofmann method.



Freshly prepared and purified samples of dienes I, II, and VI were subjected to a number of free radical initiated polymerizations using conventional emulsion recipes. Some of the polymerization results are summarized in the table below.

Monomer	Conversion (100%) to Polymer	M.P., °C.	Solubility	% 1,4-units
 (I)	< 24 hours	amor.	sol.	80
 (II)	"	"	"	94
 (VI)	> 60	148-152°	insol.	> 90

While the rates of polymerization of monomers I and II were fast, that of monomer VI was comparatively slow. Homopolymer products from VI were either oils or brittle, powdery solids depending upon the polymerization time. The solid homopolymers from VI were highly crystalline as evidenced by their complete insolubility in all common organic solvents and high melting points. The comparatively narrow melting point range indicates absence of extensive crosslinking. Infrared spectra of the solid polymers lacked terminal methylene absorption and indicated all cis-1,4-units.

Since the diene VI was prepared and purified by the same methods used for dienes I and II, its extremely slow rate of polymerization appears to be peculiar to the six-membered ring system. In addition to the increased steric effect present in going from the five-carbon to





the six-carbon cyclic monomer a more significant structural difference is the spatial relationship of the exocyclic double bonds. In I and II, which polymerize rapidly, the exocyclic double bonds are forced to be coplanar by the steric requirements of the cyclobutane and cyclopentane rings. In monomer VI, however, there is a deviation from coplanarity of the double bond system when the cyclohexane ring is in the chair conformation. The angle between the planes of the double bonds approaches  $60^\circ$  in this conformation. The ultraviolet absorption maxima of the dienes may be taken as a measure of the relative coplanarity of the double bond system, as with the 1,2-diketone system. Monomer VI has a maximum absorption about 30 m $\mu$  lower than the maxima for monomers I and II.

This non-coplanarity of the conjugated system would be expected to decrease the reactivity of the monomer toward 1,4-addition. Free radical addition to one of the exocyclic methylene groups and resultant formation of the endocyclic double bond (1,4-addition) requires twisting the ring system so that the originally non-planar methylene carbon atoms become coplanar. Although VI in the less stable boat conformation has the double bonds coplanar and the energy difference between the chair and boat forms of cyclohexane only amounts to about 5.6 kcal., (10) this energy difference included in the activation energy can reasonably account for the slower rate of polymerization. This marked decrease in monomer reactivity has also been encountered in the substituted 1,2-dimethylenecyclohexanes, 4-neopentyl-1,2-dimethylenecyclohexane and 1,2-dimethylene-4-methylcyclohexane.

In addition to the decreased reactivity, VI is anomalous in that it gives a highly crystalline homopolymer while I and II give amorphous homopolymers when polymerized under the same conditions. A rational explanation can be proposed based on steric considerations of the polymer chains in each of the above polydienes. If the main chains of the polymers are placed on an extended plane they will appear as in the figure below.



Consideration of chain and ring dimensions indicate that in the homopolymer of I ( $n=2$ ) there is no steric overlap of rings in adjacent 1,4-units. As a result chain segments have a high degree of mobility. In the polymer of II ( $n=3$ ), the five-membered rings on adjacent units just start to overlap and chain segments have decreased mobility with respect to segments in poly-I. Going from the five-membered to the six-membered ring polymer unit ( $n=4$ ) involves a 21% increase in ring diameter. As a result there is a great degree of steric overlap of rings on adjacent units in poly-VI. In the extended chain conformation, mobility of chain segments is therefore virtually impossible. This steric situation is analogous to that which would exist in the extended chain conformations of isotactic polymers of  $\alpha$ -olefins ( $\text{CH}_2=\text{CHR}$ ) having bulky R-groups. However, Natta (11) has shown that in the formation of such isotactic chains, rotation occurs between successive units to avoid overlap of adjacent R-groups. The rotation is carried out uniformly in one direction and the polymeric chain is wound into a helix. The helix which is formed does not arise during





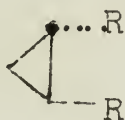
crystallization but is the property of the chain imposed by steric factors. For example, in the isotactic polymers of 1-butene, styrene and 5-methyl-1-hexene each monomer unit is turned  $120^\circ$  from the axes of the adjacent units. A helix with an identity period of three units is formed. The resulting conformation is gauche and is the one with minimum interference between substituents and hydrogen atoms. Such helices can be considered bulky "rigid rods". Flory (12) has discussed the statistical mechanics of rigid rod-like polymers and has concluded that such rigidity favors crystallization. The high degree of crystallinity of isotactic polymers has been attributed to this factor (13). The polymer chains derived from 1,2-dimethylenecyclohexane can be considered pseudo-isotactic in that they consist of successive units of identical configurations (1,4-cis). Thus it is reasonable to expect that in the polymerization of diene VI propagation also gives helicoidal chains with a minimum of steric overlap between rings. Molecular models show that the bulky six-membered rings in a chain of poly-VI can be nicely accommodated in a chain helix of the gauche conformation with an identity period of three monomer units.

As in the case of the isotactic polymers the spiral chains in poly-VI would be rigid rods and would favor crystallinity. In the polymerization of VI, the slow propagation rate observed, where transition states capable of orientation can have suitable lifetimes, would aid in the formation of the sterically favorable chain helices.

#### (B) Precursors of Dimethylenecyclopropane and Trimethylenecyclopropane

Certain unsaturated cyclopropane derivatives have been predicted, on the basis of molecular orbital calculations, to have pseudoaromatic or non-classical aromatic character (14). The ultimate test of these predictions must eventually lie in the synthesis and study of the compounds in question. Recently, the synthesis and characterization of a number of derivatives obtained from two of the more readily accessible cyclopropane diacids, cyclopropane-trans-1,2-dicarboxylic acid and Feist's acid, were carried out. Included in the derivatives are the precursors of 1,2-dimethylenecyclopropane and 1,2,3-trimethylenecyclopropane.

The following derivatives of cyclopropane-trans-1,2-dicarboxylic acid were obtained:



$R = \text{CH}_2\text{OAc}, \text{CH}_2\text{OH}, \text{CH}_2\text{Br}, \text{CH}_2\text{OTs}, \text{COCl}, \text{CONH}\phi, \text{CONMe}_2 \text{ and } \text{CH}_2\text{NMe}_2$

The last compound ( $R = \text{CH}_2\text{NMe}_2$ ) was obtained from the diacid ( $R = \text{CO}_2\text{H}$ ) in 71% overall yield. This diamine is the precursor, via the amine oxide or Hofmann eliminations, of the simplest conjugated exocyclic diene, 1,2-dimethylenecyclopropane ( $R = =\text{CH}_2$ ).





The following derivatives of Feist's acid were prepared:



R = COCl, CONH $\emptyset$ , CONMe<sub>2</sub> and CH<sub>2</sub>NMe<sub>2</sub>.

The last compound (R = CH<sub>2</sub>NMe<sub>2</sub>) was obtained from Feist's acid (R = CO<sub>2</sub>H) in 43% yield and is the precursor trimethylenecyclopropane (R = =CH<sub>2</sub>).

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1911

CHICAGO, ILL.

TO THE PRESIDENT OF THE UNIVERSITY OF CHICAGO

Dear Sir: I have the honor to acknowledge the receipt of your letter of the 14th inst. and in reply to inform you that the same has been forwarded to the proper authorities for their consideration.

Very respectfully,

Yours very truly,  
[Signature]  
[Name]  
[Title]  
[Address]  
[City]  
[State]  
[Country]

Enclosed for you are the following documents:

- 1. A copy of the report of the Committee on the subject of the proposed change in the curriculum of the College of Arts and Sciences.
- 2. A copy of the report of the Committee on the subject of the proposed change in the curriculum of the College of Engineering.
- 3. A copy of the report of the Committee on the subject of the proposed change in the curriculum of the College of Divinity.
- 4. A copy of the report of the Committee on the subject of the proposed change in the curriculum of the College of Medicine.
- 5. A copy of the report of the Committee on the subject of the proposed change in the curriculum of the College of Law.
- 6. A copy of the report of the Committee on the subject of the proposed change in the curriculum of the College of Commerce.
- 7. A copy of the report of the Committee on the subject of the proposed change in the curriculum of the College of Education.
- 8. A copy of the report of the Committee on the subject of the proposed change in the curriculum of the College of Fine Arts.
- 9. A copy of the report of the Committee on the subject of the proposed change in the curriculum of the College of Music.
- 10. A copy of the report of the Committee on the subject of the proposed change in the curriculum of the College of Architecture.

# THE STEREOCHEMISTRY OF THE BICYCLO[3.3.0]OCTANES

Reported by L. Haynes

September 22, 1958

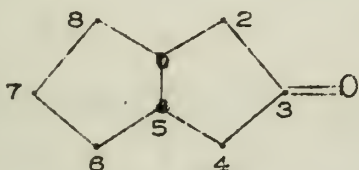
This seminar abstract will present a survey of work which has established the stereochemistry of homocyclic and several heterocyclic bicyclo[3.3.0]octanes. The Senecio alkaloids which possess the pyrrolizidine nucleus (I) will not be discussed since the subject has been amply reviewed by several authors (1,2,3,4,5).



I

## Homocyclic Bicyclo[3.3.0]octanes

Linstead and Meade were the first to synthesize successfully cis- and trans-bicyclo[3.3.0]octan-3-one (6). The cis-isomer (II) was



II



III

obtained by a Dieckmann cyclization of the diethyl ester of cis-cyclopentane-1,2-diacetic acid and by heating the acid at 280-290° over barium oxide. Dieckmann cyclization of the diethyl ester of trans-cyclopentane-1,2-diacetic acid did not yield the desired ketone. However, heating of the trans-acid at 320° over barium oxide did yield trans-bicyclo[3.3.0]octan-3-one (III). Barrett and Linstead (7) established that the trans-cyclopentane-1,2-diacetic acid was actually the racemate by isolating a levo trans-acid via its brucine salt. Trans-bicyclo[3.3.0]octan-3-one was reduced to trans-bicyclo[3.3.0]octane using the Wolff-Kishner method.

Cook and Linstead synthesized cis-bicyclo[3.3.0]octan-2-one by heating cis-cyclopentane-1-carboxylic-2-propionic acid at 280-290° over barium oxide and also via the Dieckmann closure of the diester (8). The resulting cis-ketone was reduced by the Wolff-Kishner method to cis-bicyclo[3.3.0]octane. When trans-cyclopentane-1-carboxylic-2-propionic acid or its ester was treated under similar conditions, only the cis-ketone could be isolated. The structure of cis-bicyclo[3.3.0]octan-2-one was verified by oxidation of the ketone to cis-cyclopentane-1-carboxylic-2-acetic acid.

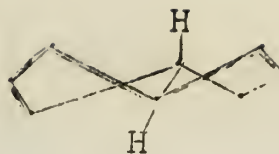
Barrett and Linstead (7) point out that cis-bicyclo[3.3.0]octane (IV) is made up of two inclined planar cyclopentane rings and would therefore be strainless, while the trans-isomer (V) is made up of two multiplanar cyclopentane rings and would be strained due to divergence from the tetrahedral arrangement. This postulate was substantiated by the finding that the trans-isomer has a heat of combustion 6 kcal. higher than that of the cis-isomer (9).







IV



V

The related dione, bicyclo[3.3.0]octane-2,6-dione (VI), was synthesized by Ruzicka, Borges de Almeida and Brack (10) by a Dieckmann reaction on 1,3,4,6-tetracarboethoxyhexane. However, no assignment was made as to the nature of the ring fusion. Cook and Linstead (8) assigned the cis configuration to this dione on the basis of their work which showed that trans-bicyclo[3.3.0]octan-2-one could not be obtained since the possibility of isomerization at the C-1 carbon existed.

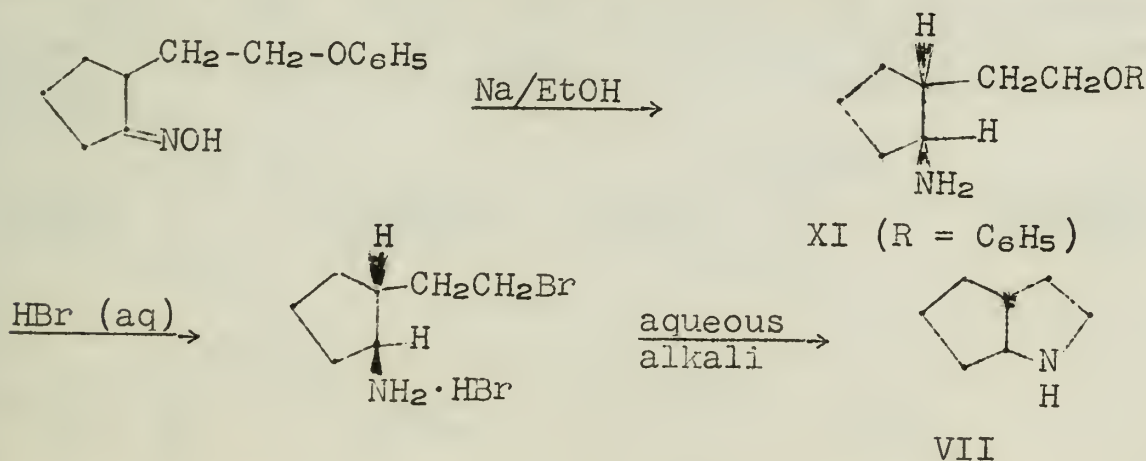


VI

### Heterocyclic Bicyclo[3.3.0]octanes

As indicated above, trans-bicyclo[3.3.0]octan-3-one was formed only under vigorous conditions. The introduction of an oxygen, nitrogen or sulfur atom into the ring may facilitate the formation of the trans system. This could be due to decreased distortion from normal bond angles and/or to the elimination of some of the hydrogen-hydrogen steric interaction.

Booth, King, Parrick and Whitehead (11) have synthesized both cis- and trans-2-azabicyclo[3.3.0]octane. The trans-isomer (VII) was synthesized by the route which Prelog and Szpilfogel (12) had used earlier. These authors assigned the trans configuration to the product based on the mode of reduction of the oxime.



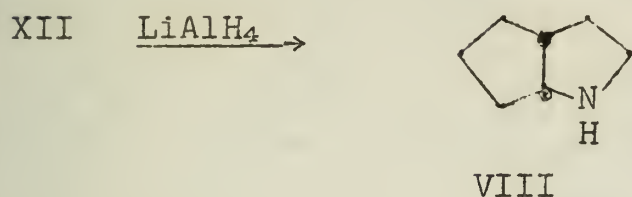
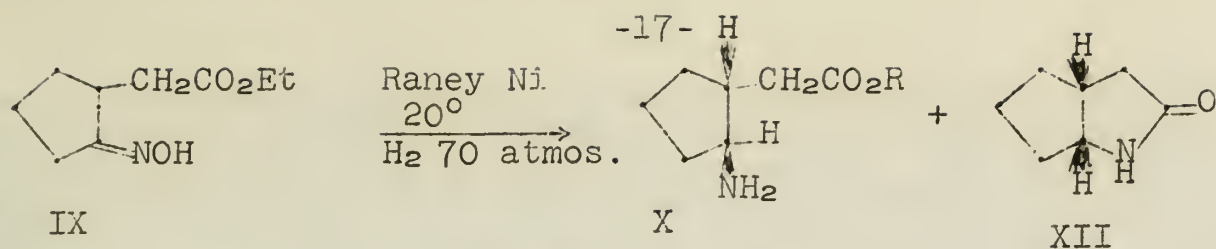
The cis-isomer (VIII) was synthesized by the following route:

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 the necessary funds to carry out its  
 policy of non-interference in the  
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The second is the fact that the  
 government has been unable to secure  
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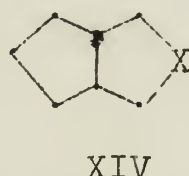
The third is the fact that the  
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 internal affairs of the country.

THE END



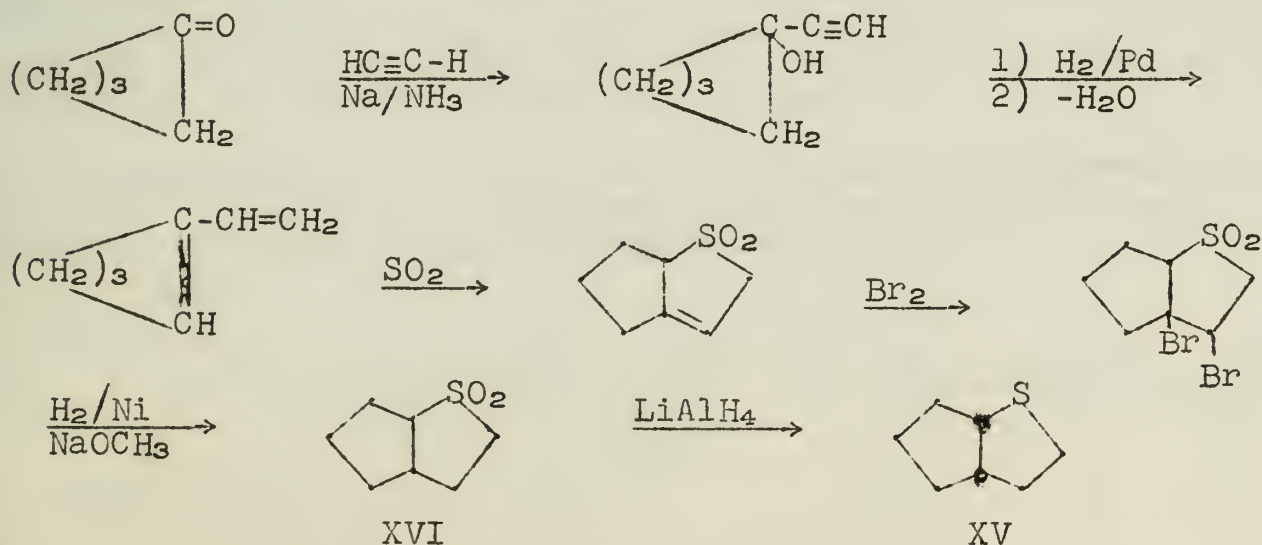
Additional evidence was presented to substantiate the configuration assigned. A by-product of the Raney nickel reduction of IX was ethyl trans-2-aminocyclopentyl acetate (X, R=Et). This compound would not form a lactam and could be reduced with lithium aluminum hydride to XI (R=H). Also the hydrochloride of the amino acid (X, R=H) was different from the hydrochloride of the amino acid derived from XII by hydrolysis.

Owen and Peto (13) synthesized cis- (XIII, X=O) and trans-3-oxabicyclo[3.3.0]octane (XIV, X=O) and cis- (XIII, X=S) and trans-3-thiabicyclo[3.3.0]octane (XIV, X=S).



The cis and trans oxygen isomers were obtained by treatment of the cis- and trans-dimethanesulfonates of 1,2-dihydroxymethylcyclopentane with aqueous potassium hydroxide at reflux. The cis and trans sulfur isomers were prepared by the action of aqueous sodium sulfide on the cis- and trans-ditoluene-*p*-sulfonates of 1,2-dihydroxymethylcyclopentane. The two thio ethers gave different sulfones.

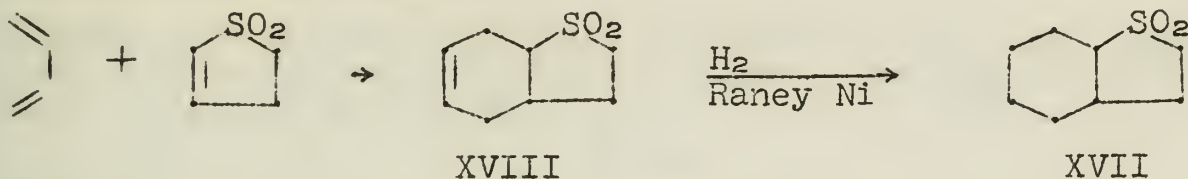
Birch, Dean, Hunter and Whitehead (14) also published a similar preparation of cis- and trans-3-thiabicyclo[3.3.0]octane. These authors, in addition, synthesized cis-2-thiabicyclo[3.3.0]octane (XV) as follows:



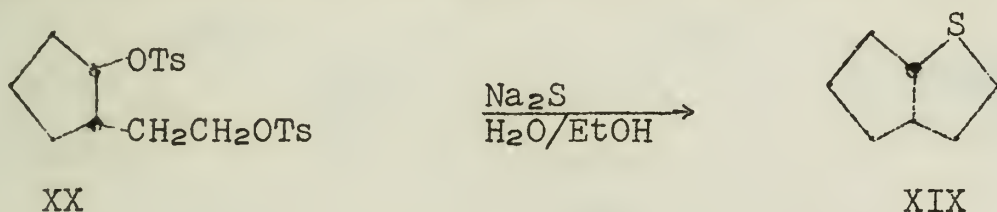




Compound XV was assigned the cis configuration since 1-thiahydrindan sulfone (XVII) prepared by the same route but using cyclohexanone as the starting ketone had the cis configuration. This was shown by an alternative synthesis from butadiene and 2,3-dihydrothiophene-1,1-dioxide to yield XVIII which, by the method of synthesis, is known to have the cis configuration. Compound XVIII was reduced to XVII using hydrogen over Raney nickel.



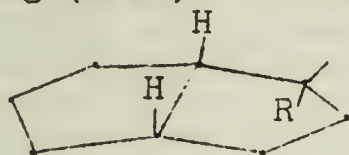
Recently Birch, Dean and Whitehead (15) reported the synthesis of trans-2-thiabicyclo[3.3.0]octane (XIX) by the action of sodium sulfide on the ditosylate of cis-(2-hydroxycyclopentyl)ethanol (XX). The trans configuration was assigned to XIX since its sulfone could be



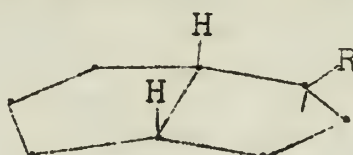
readily isomerized, under mild conditions, to the sulfone of the cis-isomer (XVI).

### The Configuration of Substituent Groups

One consequence of the nature of the cis-bicyclo[3.3.0]octane system is that a substituent group can have one of two configurations: endo - under the fold of the ring (XXI) or exo - above the fold of the ring (XXII). It can be expected that due to steric interaction an



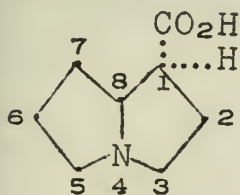
XXI



XXII

endo-isomer would be less stable than the exo-isomer, as with axial vs. equatorial substitution in the cyclohexane series. The following discussion will center on the use of this concept to determine the configuration of various bicyclo[3.3.0]octanes.

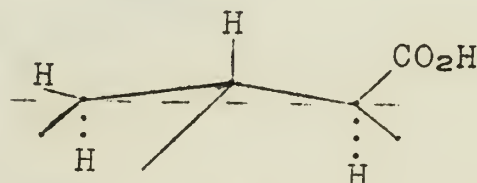
Leonard (16) discusses this with regard to 1-pyrrolizidinecarboxylic acid (XXIII). This acid can be represented in its endo configuration by A and in its exo configuration by B.



XXIII



A

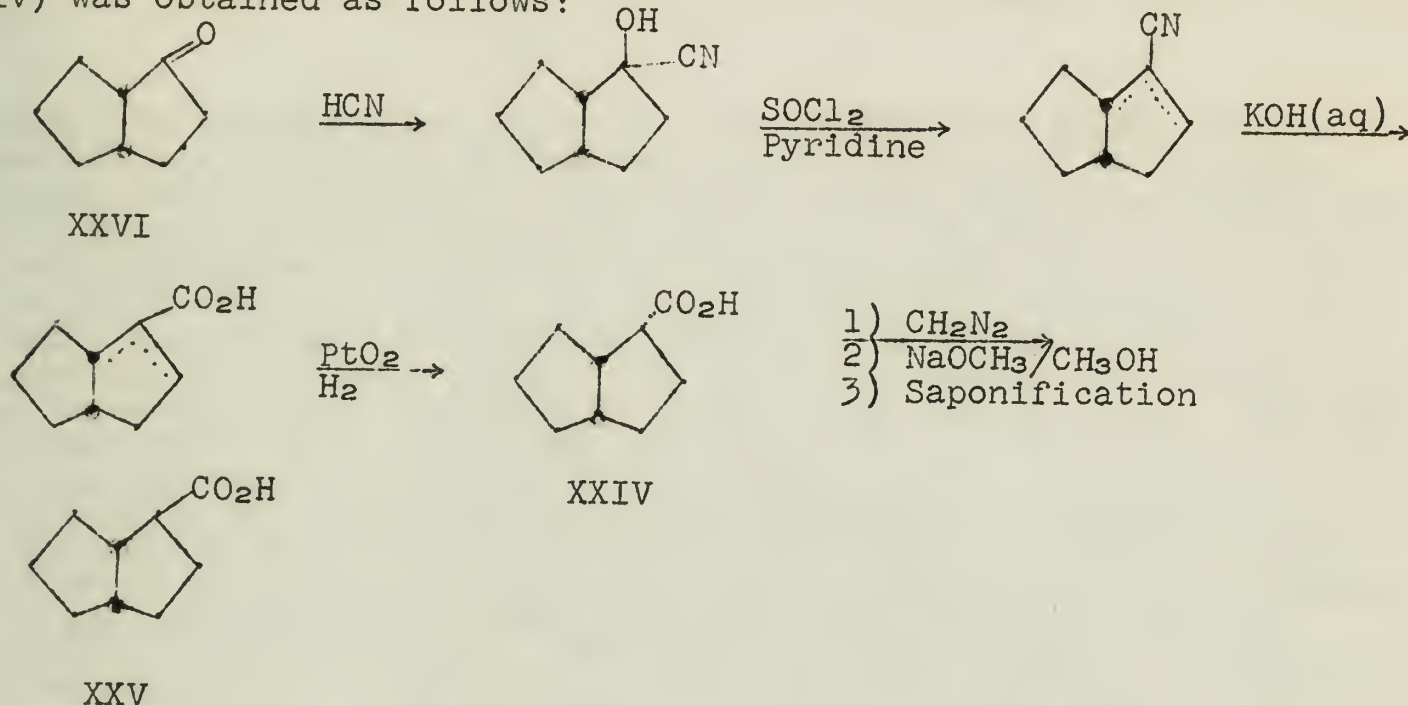


B



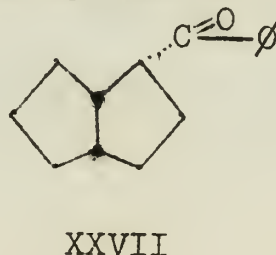
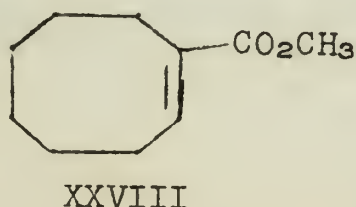
Since in A there is repulsion between the C-1 carboxyl and the C-7 hydrogen, while in B there is only hydrogen-hydrogen interaction, the equilibrium, under epimerizing conditions, should favor B which has trans-1,8-hydrogens. This would explain the isolation, in chromic acid oxidation, of one acid from the 1-hydroxymethylpyrrolizidines possessing trans-1,8-hydrogens and two acids from the 1-hydroxymethylpyrrolizidines having cis-1,8-hydrogens.

Granger, Nau and Nau (17) have prepared the exo- and endo-2-carboxy- and 2-amino-cis-bicyclo[3.3.0]octanes. The endo-2-carboxy isomer (XXIV) was obtained as follows:



The methyl ester of XXIV was heated with sodium methoxide in methanol and then saponified to give the exo-isomer (XXV). The corresponding endo and exo amines were obtained by Raney nickel reduction of the oxime of cis-bicyclo[3.3.0]octan-2-one (XXVI). The stereochemistry of the two amines obtained was determined by comparison with the amines obtained from the exo and endo acids by the Schmidt reaction, which preserves the stereochemistry of the starting acid. In much the same way these authors later prepared the exo- and endo-3-carboxy- and 3-amino-cis-bicyclo[3.3.0]octanes (18). Configuration assignments were again based on the conversion of the endo acid to the exo acid.

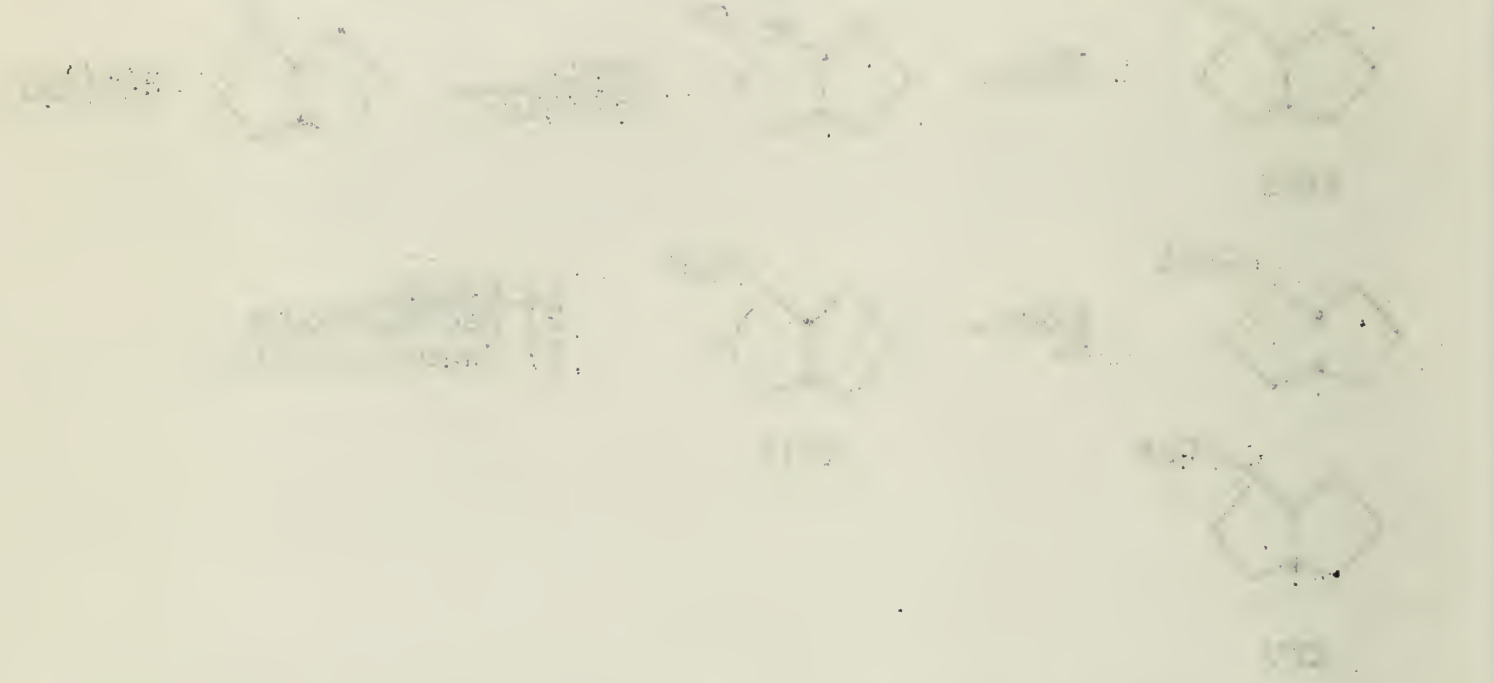
Cope and Brown in 1958 (19) isolated phenyl endo-cis-bicyclo[3.3.0]oct-2-yl ketone (XXVII) from the reaction of phenylmagnesium bromide in 10% molar excess at -10° with methyl cyclooctene-1-carboxylate (XXVIII). The ring structure of XXVII was established by its conversion to cis-bicyclo[3.3.0]octan-2-one by a Barbier-Wieland degradation. The endo configuration of the benzoyl group was determined by synthesis of the ketone (XXVII).





The first part of the paper deals with the general properties of the system. It is shown that the system is stable and that the solution is unique. The second part of the paper deals with the numerical solution of the system. It is shown that the numerical solution is stable and that the error is small.

The third part of the paper deals with the analytical solution of the system. It is shown that the analytical solution is stable and that the error is small.



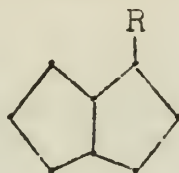
The fourth part of the paper deals with the experimental results. It is shown that the experimental results are in good agreement with the theoretical results. The fifth part of the paper deals with the conclusions. It is shown that the system is stable and that the solution is unique.

The sixth part of the paper deals with the references. It is shown that the references are in good agreement with the theoretical results. The seventh part of the paper deals with the acknowledgments. It is shown that the acknowledgments are in good agreement with the theoretical results.





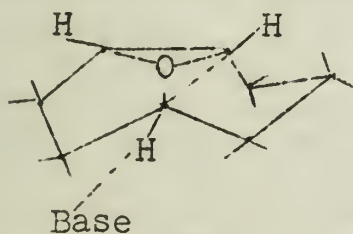
These exo and endo phenyl ketones were synthesized from the corresponding acids which were prepared independently by Cope and Brown using essentially the same route as Granger, Nau and Nau (17). Cope and Brown assigned structures to the unsaturated nitrile (XXIX, R=CN) and to the unsaturated acid (XXIX, R=COOH). Both were considered to



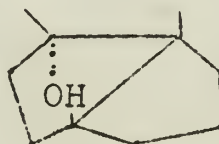
XXIX

possess 1(2)-unsaturation since the infrared spectra showed the presence of a conjugated system and a double bond, but no olefinic hydrogen band at  $3030\text{ cm}^{-1}$ . The nitrile (XXIX, R=CN) was reduced over palladium-on-carbon to give the saturated nitrile which was hydrolyzed in refluxing ethanolic potassium hydroxide to yield exo-cis-2-carboxy-bicyclo[3.3.0]octane (XXV). The exo configuration was assigned since the acid was obtained by alkaline hydrolysis which would be expected to give the more stable isomer. The melting point of the amide of this acid checks with that obtained by Granger, Nau and Nau (17). The exo acid was converted to phenyl exo-cis-bicyclo[3.3.0]oct-2-yl ketone by reaction of the acid chloride with diphenylcadmium. By contrast, the melting point of the 2,4-dinitrophenylhydrazone of the exo-ketone did not check with that of the 2,4-dinitrophenylhydrazone of the ketone produced by the action of phenylmagnesium bromide on XXVIII. Palladium-on-carbon hydrogenation of XXIX (R=COOH) gave endo-cis-2-carboxy-bicyclo[3.3.0]octane (XXIV). The endo acid was converted, as described for the exo acid, to phenyl endo-cis-bicyclo[3.3.0]oct-2-yl ketone, which was identical with the ketone isolated from the reaction of phenylmagnesium bromide with XXVIII. The endo-acid could be converted to the exo-acid by heating it with concentrated hydrochloric acid or with ethanolic potassium hydroxide. The cis-fusion of the synthetic phenyl ketones was demonstrated by perbenzoic acid oxidation, which gave the known endo- and exo-cis-bicyclo[3.3.0]octan-2-ols (21).

Cope, Lee and Petree have investigated the transannular reactions of cis- and trans-cyclooctene oxide (20), and their alkaline ring opening is germane to the present discussion. When cis-cyclooctene oxide (XXX) is treated in refluxing benzene with lithium diethylamide or phenyllithium, endo-cis-bicyclo[3.3.0]octan-2-ol (XXXI) is formed.



XXX

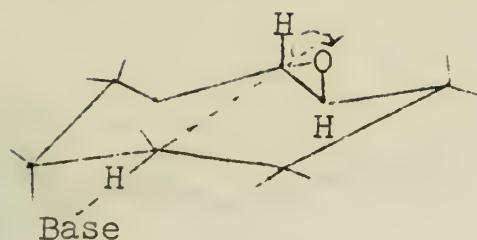


XXXI

When trans-cyclooctene oxide (XXXII) is heated in refluxing benzene with lithium diethylamide, exo-cis-bicyclo[3.3.0]octan-2-ol (XXXIII) results.







XXXII

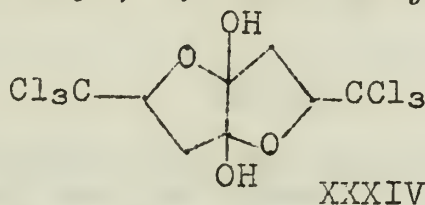


XXXIII

The assigned configurations were validated by the synthesis of these two alcohols. Cope, Brown and Petree (21) reduced cis-bicyclo[3.3.0]octan-2-one with several reagents and obtained in each case endo-cis-bicyclo[3.3.0]octan-2-ol (XXXI). The configuration was shown to be endo by conversion of endo-cis-2-carboxybicyclo[3.3.0]octane to methyl endo-cis-bicyclo[3.3.0]oct-2-yl ketone, which was then converted to XXXI by the action of perbenzoic acid followed by saponification. The exo-alcohol (XXXIII) was prepared in like manner from exo-cis-2-carboxybicyclo[3.3.0]octane. The endo-alcohol could be converted to the exo-alcohol by the action of tetraethylammonium acetate on its tosylate followed by saponification. To prove that the exo-alcohol prepared in this manner had an unreacted carbon skeleton, it was oxidized to cis-bicyclo[3.3.0]octan-2-one by N-bromosuccinimide. The exo-alcohol could not be converted to the endo-alcohol through its tosylate or acetate.

Cope, Grisar and Peterson (22) have isolated endo- and exo-bicyclo[3.3.0]octan-2-ol from the reaction of formic acid with cis-cis-1,5-cyclooctadiene and from the solvolysis of 4-cycloocten-1-yl brosylate in acetic acid containing sodium acetate. Cope, Moon and Peterson (23) also obtained these alcohols from the solvolysis of the ditosylates of cis-1,2- and cis-1,4-cyclooctanediol. A transannular reaction involving a carbonium ion or a participating double bond can account for the observed products.

Through the use of physical and chemical evidence Leonard, Little and Kresge (24) were able to determine the structure of chloretyl: 3,7-di(trichloromethyl)-2,6-dioxabicyclo[3.3.0]octane-1,5-diol (XXXIV).



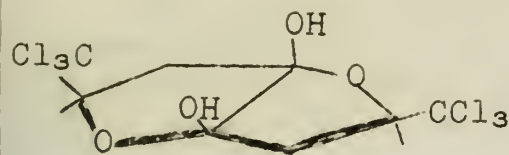
XXXIV

The reaction of biacetyl with chloral gave an  $\alpha$ - and a  $\beta$ -modification of chloretyl. The  $\alpha$ -form had a hydroxyl band at  $3480\text{ cm}^{-1}$ ; the  $\beta$ -form, at  $3450\text{ cm}^{-1}$ . The tetrahydrofuran nuclei were indicated by characteristic absorption bands in the  $990$  to  $1100\text{ cm}^{-1}$  region. The nuclear magnetic resonance spectrum showed the ratio of 1:1:2 for the different types of hydrogen: *i.e.*, two hydroxyl hydrogens, two  $\text{CHCCl}_3$  hydrogens and four methylene hydrogens. The hemiketal hydroxyl function was indicated by the high frequency of the carbonyl stretching band ( $1765\text{ cm}^{-1}$ ) of  $\alpha$ -chloretyl monoacetate. Additional chemical evidence is presented to support structure XXXIV for chloretyl.

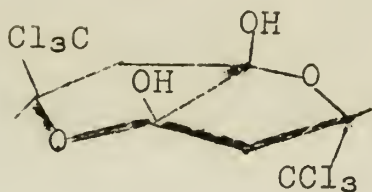
Since cis-bicyclo[3.3.0]octane is more stable than the trans-isomer (9), chloretyl was tentatively assigned the three possible configurations XXXV, XXXVI and XXXVII.



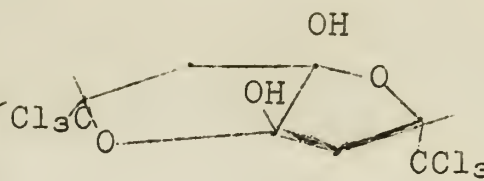




XXXV  
cis-cis-cis



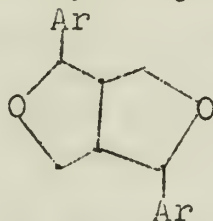
XXXVI  
cis-cis-trans



XXXVII  
trans-cis-trans

Isomer XXXVII is least favored since the trichloromethyl groups are in steric opposition. In addition the infrared hydroxyl stretching frequency should be in the normal hydroxyl range, but both isomers isolated had infrared hydroxyl bands at lower than normal frequency. The authors conclude, on the basis of several examples from the literature, that the lowering of frequency is due to the proximity of chlorine to hydroxyl hydrogen. The determination of the infrared spectra of dilute solutions of the  $\alpha$ - and  $\beta$ -forms in benzene showed a  $3550\text{ cm}^{-1}$  hydroxyl band for the  $\beta$ -form and a  $3510\text{ cm}^{-1}$  hydroxyl band for the  $\alpha$ -form. Therefore structure XXXV was assigned to  $\alpha$ -chloretyl since effectively two chlorines exert an attraction for the hydroxylic hydrogens and structure XXXVI to  $\beta$ -chloretyl since only one chlorine exerts an attraction for the hydroxylic hydrogens. The presence of 80% of  $\alpha$ -chloretyl in an equilibrium mixture indicates that it is the more stable isomer. This is consistent with the structure assigned on the basis of the infrared findings.

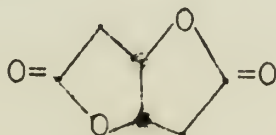
The 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes (XXXVIII) are naturally occurring lignans. These compounds are also named as tetrahydrofurofurans. The aryl groups are, in general, substituted on the 3',4'-positions by methoxy, hydroxy or methylenedioxy groups. Hearon



XXXVIII

and MacGregor reviewed this field in 1955 (25) but the stereochemistry of these compounds was not known. A brief review of how the general structure of these compounds was determined will be useful.

In 1947 Erdtman and Gripenberg (26) were able to isolate the di- $\gamma$ -lactone of  $\alpha,\beta$ -bis(hydroxymethyl)succinic acid (XXXIX) from the nitric acid oxidation of dibromopinoresinol dimethyl ether. Since the dilactone thus obtained was optically active, the bridge hydrogens were considered to be cis. This dilactone, also isolated from other lignans of this group, was synthesized to identify conclusively the dilactone from the degradation.



XXXIX



The first part of the report deals with the general principles of the method. It is shown that the method is applicable to a wide range of cases, and that it is capable of giving results which are in good agreement with those obtained by other methods. The second part of the report describes the details of the method, and gives a number of examples of its application. The third part of the report discusses the results of the method, and compares them with those obtained by other methods. It is shown that the method is capable of giving results which are in good agreement with those obtained by other methods, and that it is capable of giving results which are in good agreement with those obtained by other methods.

The results of the method are compared with those obtained by other methods, and it is shown that the method is capable of giving results which are in good agreement with those obtained by other methods. The method is capable of giving results which are in good agreement with those obtained by other methods, and it is shown that the method is capable of giving results which are in good agreement with those obtained by other methods.

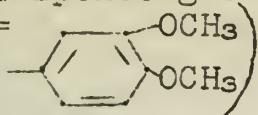


FIG. 1

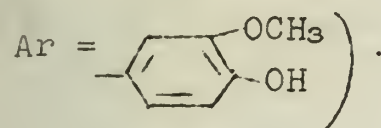
The results of the method are compared with those obtained by other methods, and it is shown that the method is capable of giving results which are in good agreement with those obtained by other methods. The method is capable of giving results which are in good agreement with those obtained by other methods, and it is shown that the method is capable of giving results which are in good agreement with those obtained by other methods. The method is capable of giving results which are in good agreement with those obtained by other methods, and it is shown that the method is capable of giving results which are in good agreement with those obtained by other methods.



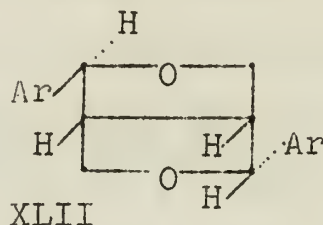
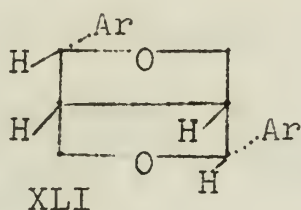
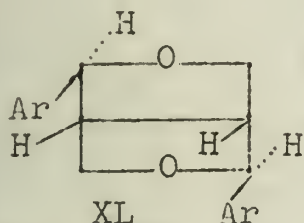
The general method used to decide whether one of these lignans is "symmetrical" (XL or XLI) or "unsymmetrical" (XLII) can be illustrated by Gripenberg's work (27) on the dimethyl ether of epipinoresinol (XLII, Ar =



and Erdtman's work (28) on pinoresinol (XL or XLI,

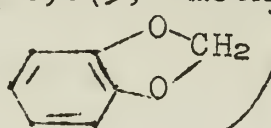


Nitration of the dimethyl ether of epipinoresinol gave two different mononitro derivatives which when brominated gave two different monobromo-mononitro derivatives. Therefore epipinoresinol



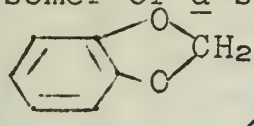
must be XLII. The "symmetry" of pinoresinol was demonstrated by the fact that ethylation of the monomethyl ether and methylation of the monoethyl ether gave the same ethylmethyl ether. Whether pinoresinol is exo (XL) or endo (XLI) has not been shown.

The first assignment of an exo or endo configuration to one of these lignans was made in 1956 by Beroza (29) who presented evidence which indicates that d-sesamin is exo-cis-2,6(3',4'-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (XL, Ar =



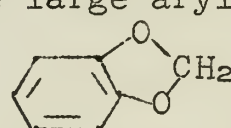
The

"symmetry" of d-sesamin had been demonstrated by Carnmalm, Erdtman and Pelchowicz (30). Beroza's postulate was based on the partial conversion of d-sesamin in refluxing ethanolic hydrochloric acid to a stereoisomer of d-sesamin called d-epiasarinin. Asarinin (XLII, Ar =



, which had been shown to be "unsymmetrical" by Erdt-

man and Pelchowicz (31), gave 1-epiasarinin when treated under the same conditions. d-Epiasarinin could be converted readily to a mixture of d-asarinin and d-sesamin. These conversions indicate that d-epiasarinin is the least stable of the three isomers. Since the endo-isomer (XLI) has the greatest steric interference due to the large aryl groups, epiasarinin was assigned structure XLI (Ar =



The other "symmetrical" structure XL (Ar = was therefore assigned to sesamin.



*[The text in this block is extremely faint and illegible, appearing to be a series of paragraphs or a list of items.]*



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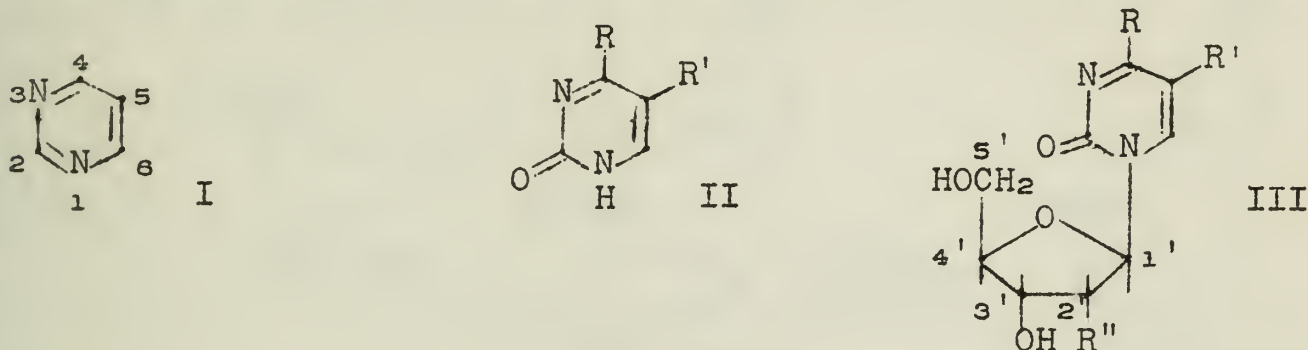
# SYNTHESIS OF PYRIMIDINE NUCLEOSIDES

Reported by J. R. Carson

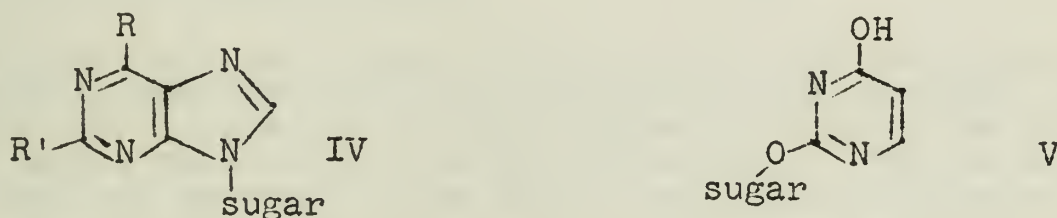
October 2, 1958

## INTRODUCTION

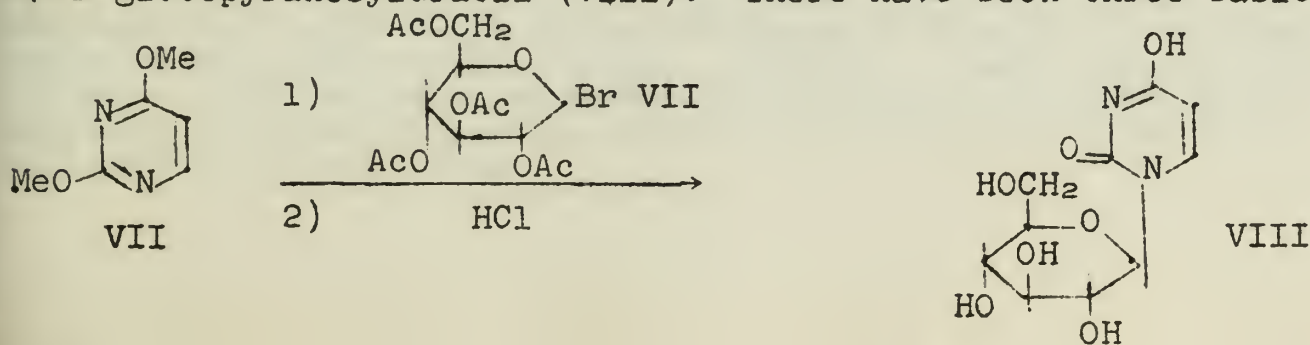
Pyrimidine nucleosides consist of a derivative of pyrimidine (I) attached to a sugar through the 1 position. The naturally occurring pyrimidines are uracil (II,  $R = OH$ ,  $R' = H$ ), cytosine (II,  $R = NH_2$ ,  $R' = H$ ), thymine (II,  $R = OH$ ,  $R' = CH_3$ ), and 5-methylcytosine (II,  $R = NH_2$ ,  $R' = CH_3$ ). The sugars usually found associated with them are



ribose and 2'-deoxyribose, although arabinose has now been found in some sponge nucleosides. Thymine, cytosine, and 5-methylcytosine occur as the deoxyribonucleosides thymidine (III,  $R = OH$ ,  $R' = CH_3$ ,  $R'' = H$ ), deoxycytidine (III,  $R = NH_2$ ,  $R' = H$ ,  $R'' = H$ ), and 5-methylcytidine (III,  $R = NH_2$ ,  $R' = CH_3$ ,  $R'' = H$ ), respectively. Uracil and cytosine occur as the ribonucleosides uridine (III,  $R = OH$ ,  $R' = H$ ,  $R'' = OH$ ) and cytidine (III,  $R = NH_2$ ,  $R' = H$ ,  $R'' = OH$ ). Nucleotides are the phosphate esters of nucleosides; nucleic acids, polymers of purine (IV) and pyrimidine nucleosides, linked by 3'- to 5'- phosphate groupings.



The field of pyrimidine nucleoside synthesis has been reviewed recently by Shaw (1). The first attempts at pyrimidine nucleoside synthesis, made by Fischer (2-4), centered on the reaction of aceto-halosugars with silver salts of hydroxypyrimidines but produced only O-glycosides (V) of the lactim form of the pyrimidines. The first successful synthesis of a pyrimidine nucleoside was that of Hilbert and Johnson (5,6), who prevented tautomerization by use of a lactim ether (VI) which they treated with acetobromoglucose (VII) to give 1-β-D-glucopyranosyluracil (VIII). There have been three basic





CHICAGO, ILLINOIS, U.S.A.

TO THE HONORABLE CHIEF OF BUREAU OF THE ARMY AND NAVY

WASHINGTON, D.C.

DEAR SIR:

I have the honor to acknowledge the receipt of your letter of the 10th inst.

and in reply to inform you that the same has been forwarded to the proper authorities for their consideration.

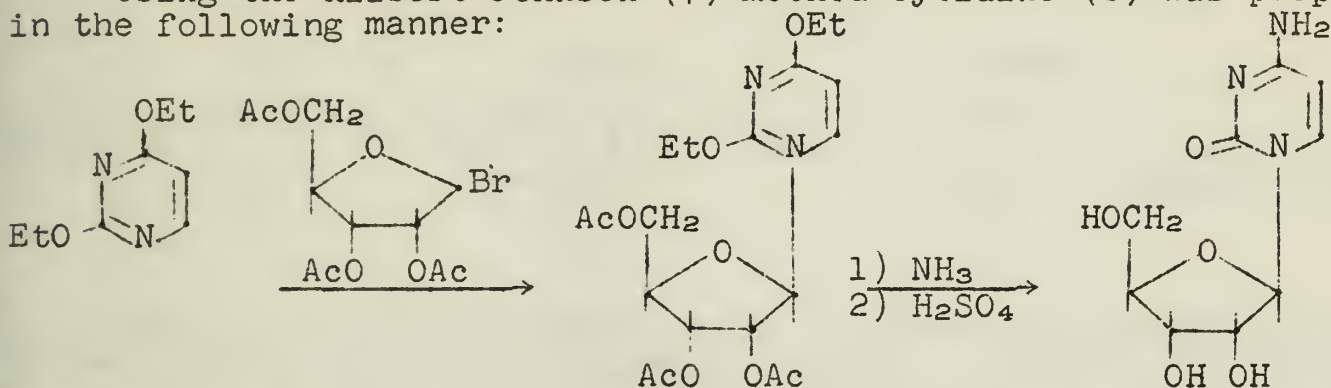
Very respectfully,  
Yours truly,  
[Signature]



approaches to pyrimidine nucleoside synthesis. The Hilbert-Johnson method falls into the category of reaction of a pyrimidine derivative with a sugar derivative. Cyclization of sugar derivatives is a new approach to nucleoside synthesis. Transformations on the sugar portion of a nucleoside have been used to prepare naturally occurring nucleosides.

# I. SYNTHESSES BY REACTION OF PYRIDMIDINE DERIVATIVES WITH SUGAR DERIVATIVES

Using the Hilbert-Johnson (7) method cytidine (8) was prepared in the following manner:

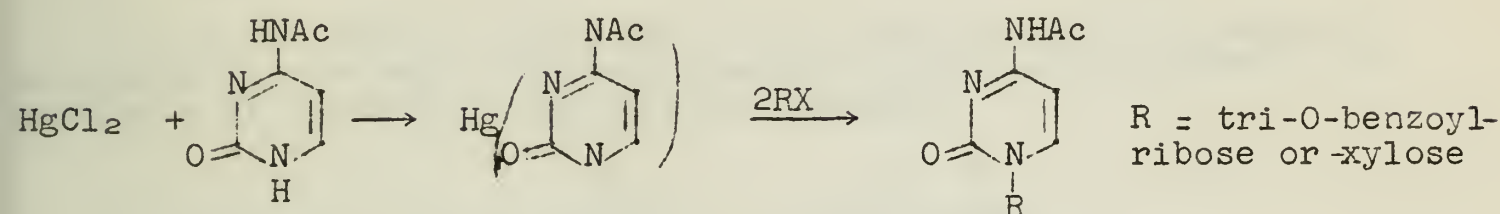
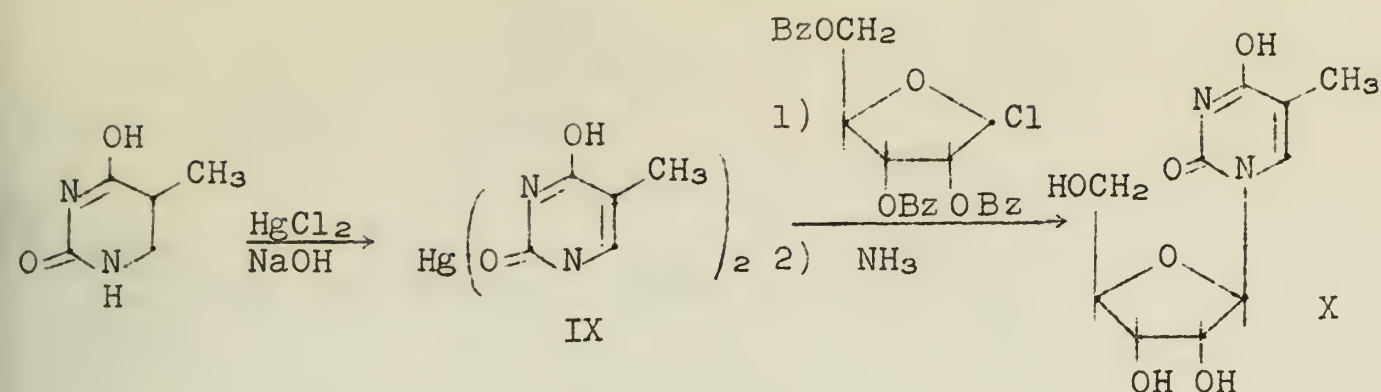


The Hilbert-Johnson method suffers from several drawbacks. In the reaction of an acetohalosugar with 2,4-diethoxypyrimidine, 4-ethoxy-1-ethyl-2-keto-pyrimidine and uracil are formed as by-products (9). Moreover, the reaction was found to give O-glycosides, identifiable by ease of hydrolysis and by spectra, on treatment with aceto-bromomannopyranose (10). Since part of the interest in nucleoside synthesis is aroused by possible chemotherapeutic value of analogs of natural compounds, it is important that a nucleoside synthesis be as general as possible. Recently (11,12) it has been found that pyrimidines with substituents in the 6-position give only O-glycosides by the Hilbert-Johnson method.

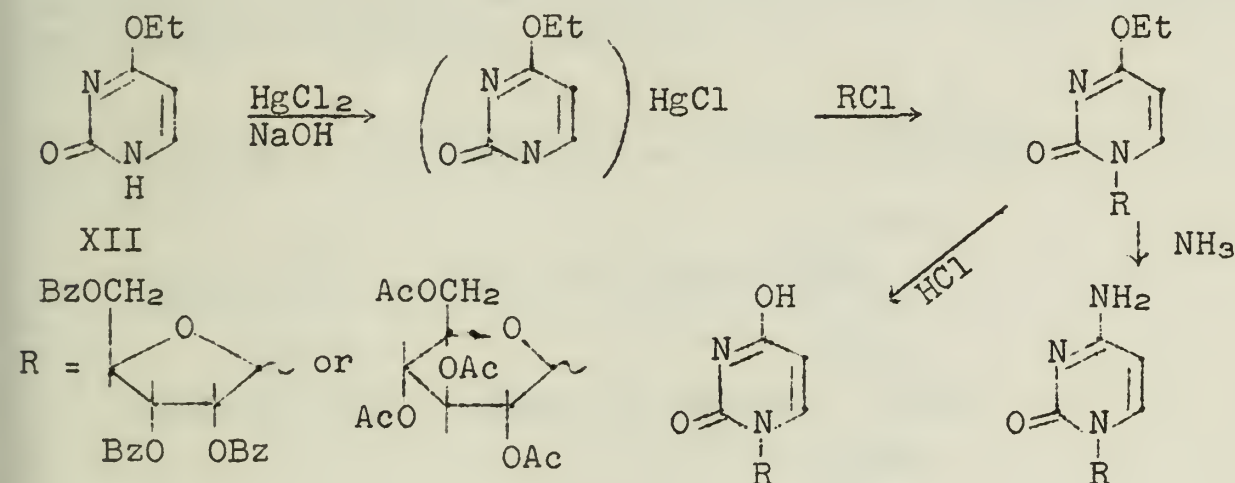
Enzymes have been found which catalyze the reversible reaction of ribose-1-phosphate (13,14) or deoxyribose-1-phosphate (15,16) with a pyrimidine to give a nucleoside and which enable the transfer of ribose from a nucleoside to a pyrimidine (17). Before the recent total chemical synthesis (see below), enzymatic synthesis offered the only pathway to analogs of natural deoxyribonucleosides.

Mercury salts of pyrimidines react with halosugar derivatives to give nucleosides. Fox and his coworkers (18) reported that when thymine was treated with the stoichiometric quantity of mercuric chloride in hot aqueous base, insoluble dithymylmercury (IX) was quantitatively precipitated. When the mercury compound was allowed to react with the acyl derivative of a 1-halosugar in refluxing xylene, a nucleoside was formed, as illustrated for 1-β-D-ribofuranosylthymine (X). Toward the preparation of cytosine nucleosides (19) a mono-chloromercuri salt of cytosine was formed but would not undergo reaction with the acylhalo sugar. However, a salt (XI) of N-acetyl-cytosine could be prepared containing equimolar quantities of pyrimidine and mercury which gave a nucleoside when treated with two equivalents of halo sugar.





The action of an acylhalo sugar on di(4-dimethylamino-2(1H)-pyrimidinone) mercury gave only O-glycosides (20). 4-Ethoxy-2(1H)-pyrimidinone (XII) gives a monochloromercuri derivative on treatment with basic mercuric chloride. This compound can be similarly used for the synthesis of cytosine or uracil nucleosides. The  $\beta$ -configuration



at the glycosidic center in cytidine has been established by X-ray crystallography (21). The synthetic uracil and cytosine nucleosides of Fox and coworkers were related to the natural ones by metaperiodate oxidation to dialdehydes showing the same rotations as those obtained from uridine and cytosine, respectively (18).

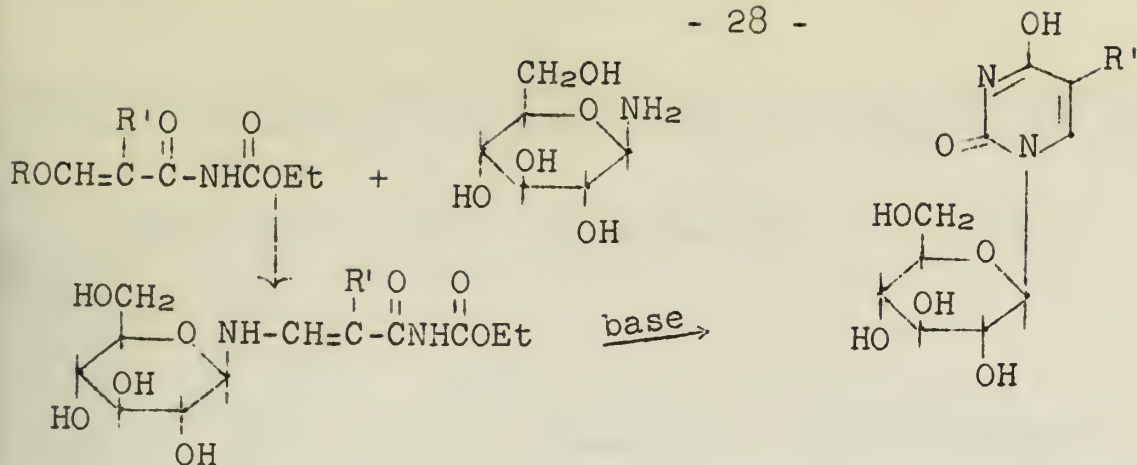
## II. SYNTHESSES BY CYCLIZATION OF SUGAR DERIVATIVES

Shaw and his coworkers have achieved the synthesis of pyrimidine nucleosides by treatment of  $\beta$ -alkoxy-N-carbethoxyacrylamides (XIII) with 1-amino sugars, followed by cyclization of the resulting  $\beta$ -glycosylamino-N-carbethoxyacrylamides (XIV) with dilute base, as shown for glucose (22,23,24).

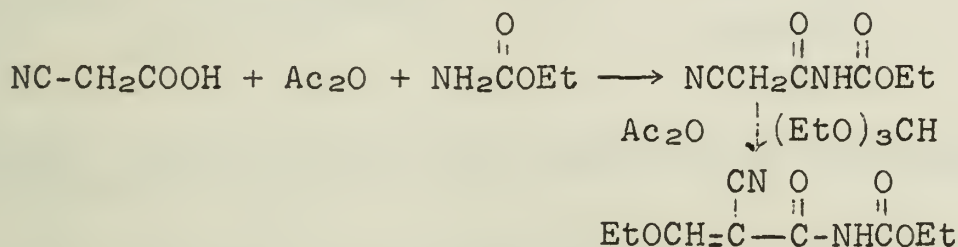




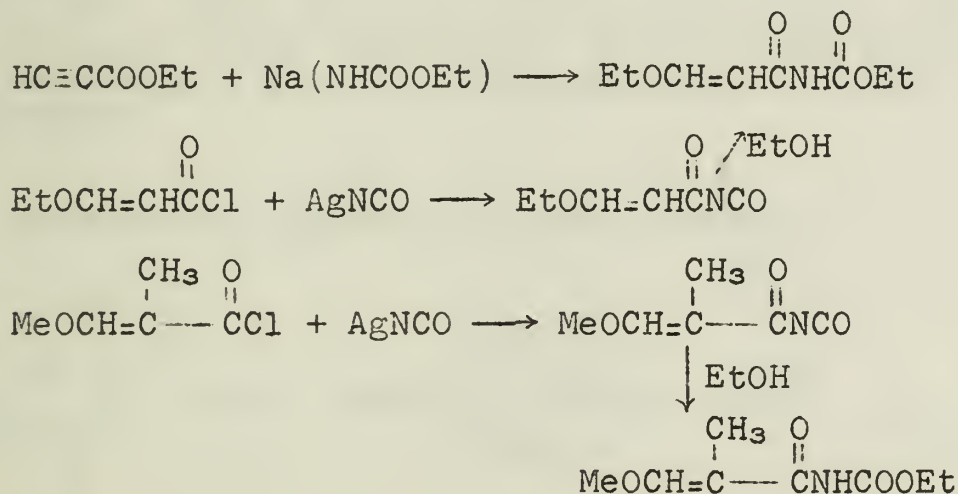




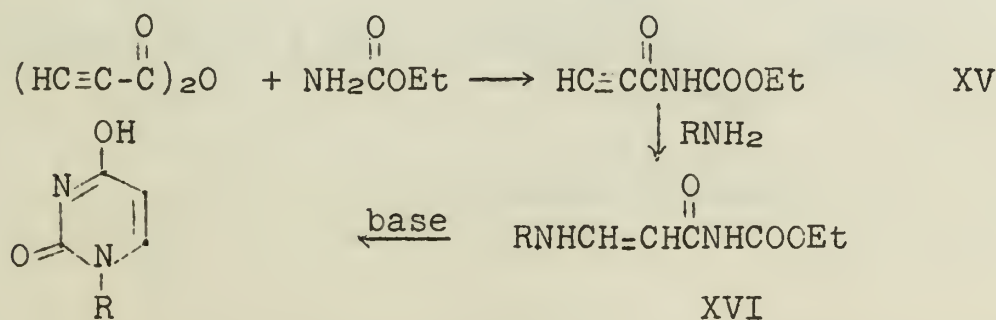
The first method (25) used for synthesizing the intermediate acrylamides gave only  $\alpha$ -cyanoacrylamides, which are unsuitable for synthesis of naturally occurring nucleosides.



Recently, methods have been published for synthesis of  $\beta$ -alkoxy-N-carbethoxyacrylamides which can be used for the synthesis of uracil and thymine nucleosides (26,27).

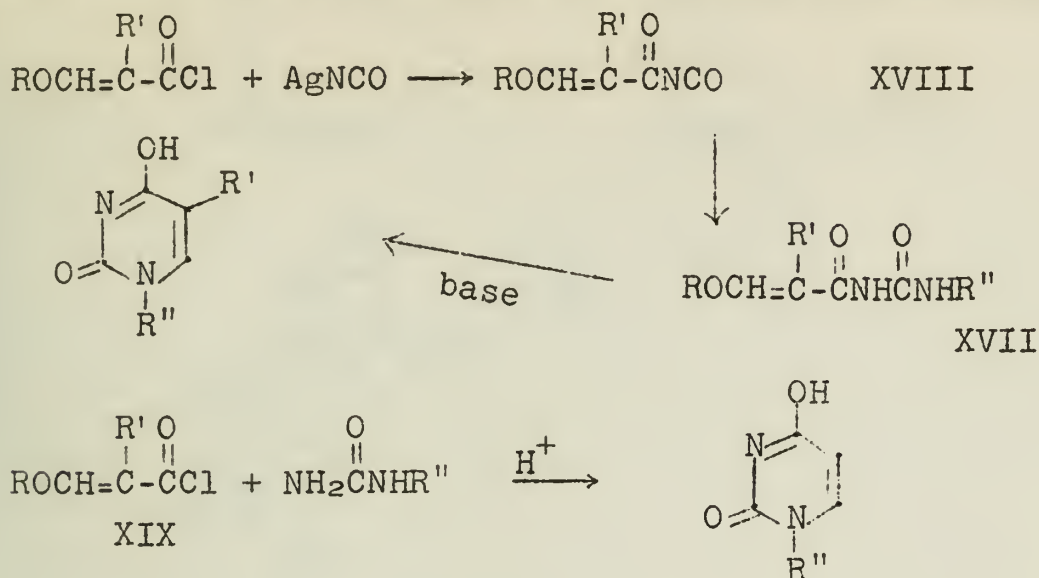


N-Carbethoxypropiolamide (XV), when treated with an amine gives a  $\beta$ -amino-N-carbethoxyacrylamide (XVI). 1-Substituted pyrimidines have been obtained by this route, but it has not yet been applied to nucleosides (24).



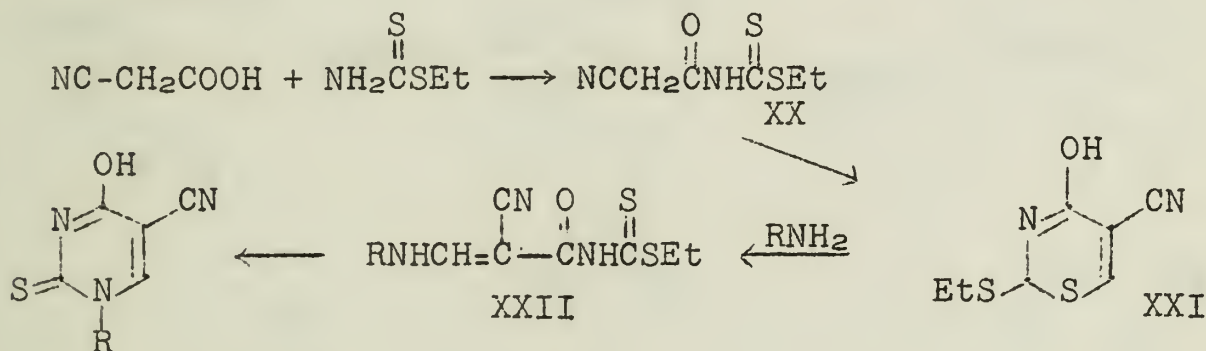


$\beta$ -Alkoxyacryloylureas (XVII), obtained from  $\beta$ -alkoxyacryloylisocyanates (XVIII) and amines, also yield 1-substituted pyrimidines.  $\beta$ -Alkoxy-

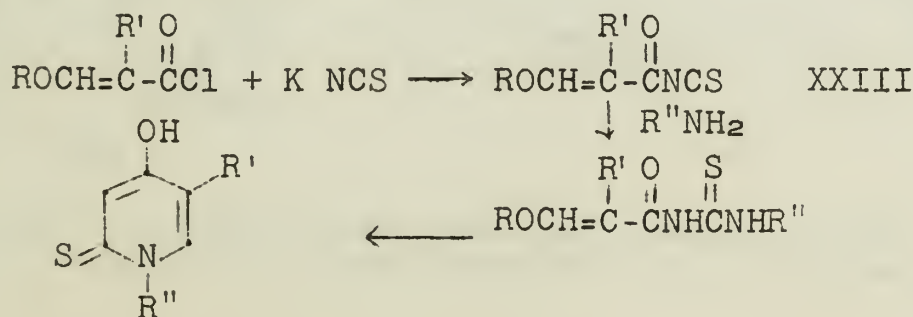


acryloyl chloride (XIX) with a substituted urea gives a 1-substituted pyrimidine directly.

The synthesis of 2-thiopyrimidine was undertaken in a manner analogous to that described above. The reaction of cyanoacetic acid with ethyl dithiocarbamate gave the expected ethyl N-cyanoacetyl-dithiocarbamate (XX), but treatment of this with ethyl orthoformate and acetic anhydride gave 5-cyano-2-ethylthio-4-oxo-1,3-thiazine (XXI) (28). This thiazine reacted with amines (28) or amino sugars (29) to give linear derivatives (XXII) which could be cyclized to the respective 1-alkyl-2-thiopyrimidines or the 2-thiopyrimidine nucleosides.



$\beta$ -Alkoxyacryloyl chlorides plus potassium thiocyanate gave  $\beta$ -alkoxyacryloylisothiocyanates (XXIII) which with amino sugars (30) gave 2-thiopyrimidine nucleosides.

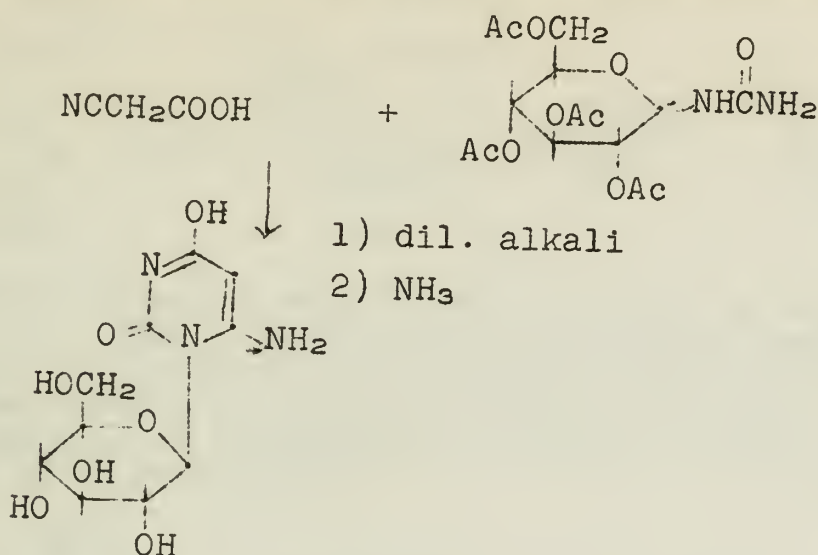


One of the standard methods of pyrimidine synthesis is that of Traube (31), involving the treatment of urea with cyanoacetic acid to



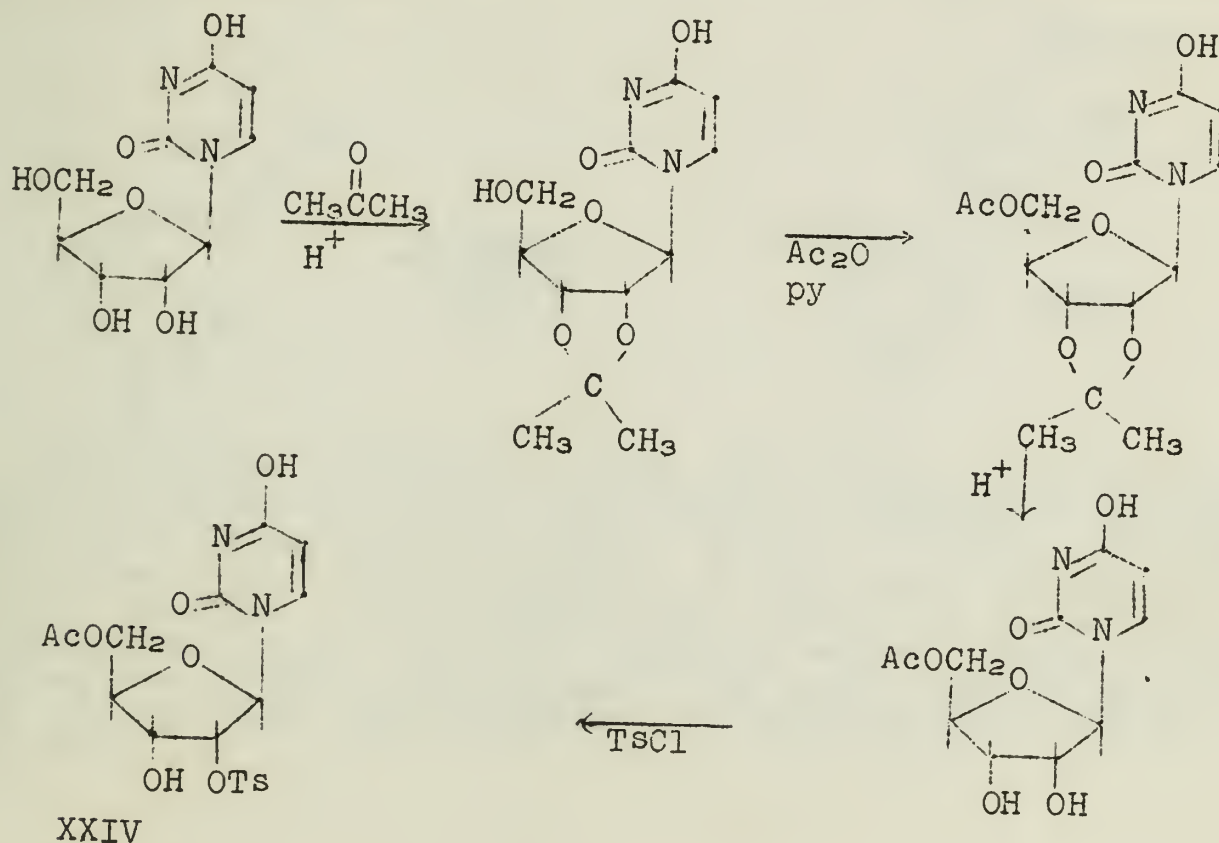


give a 6-aminopyrimidine. The reaction has now been extended by Goodman (32) to the synthesis of 6-aminopyrimidine nucleosides:



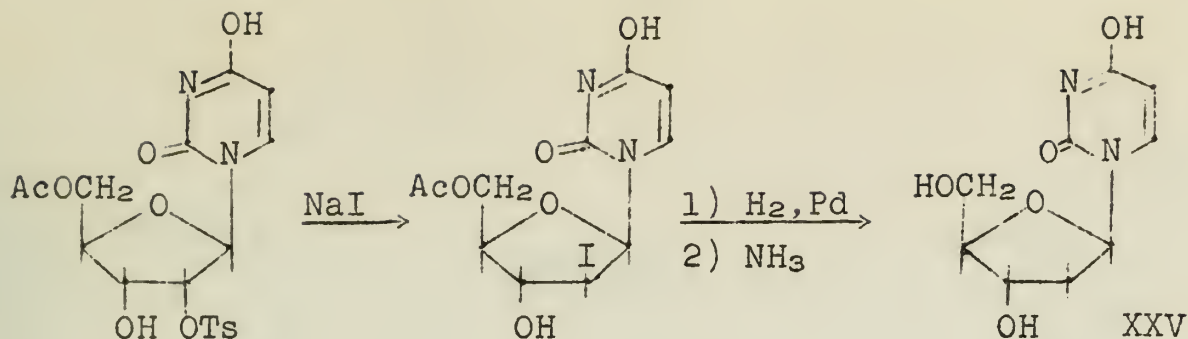
### III. REACTIONS OF THE SUGAR PORTION OF PYRIMIDINE NUCLEOSIDES

Unavailability of 1-halo or amino derivatives of 2-deoxyribose has stalled the synthesis of naturally occurring 2'-deoxyribonucleosides. Recently, two methods have been devised for transforming ribonucleosides to deoxyribonucleosides. Todd and his coworkers (33) used 5'-O-acetyl-2'-O-p-toluenesulfonyluridine (XXIV), which was obtained as follows (34):

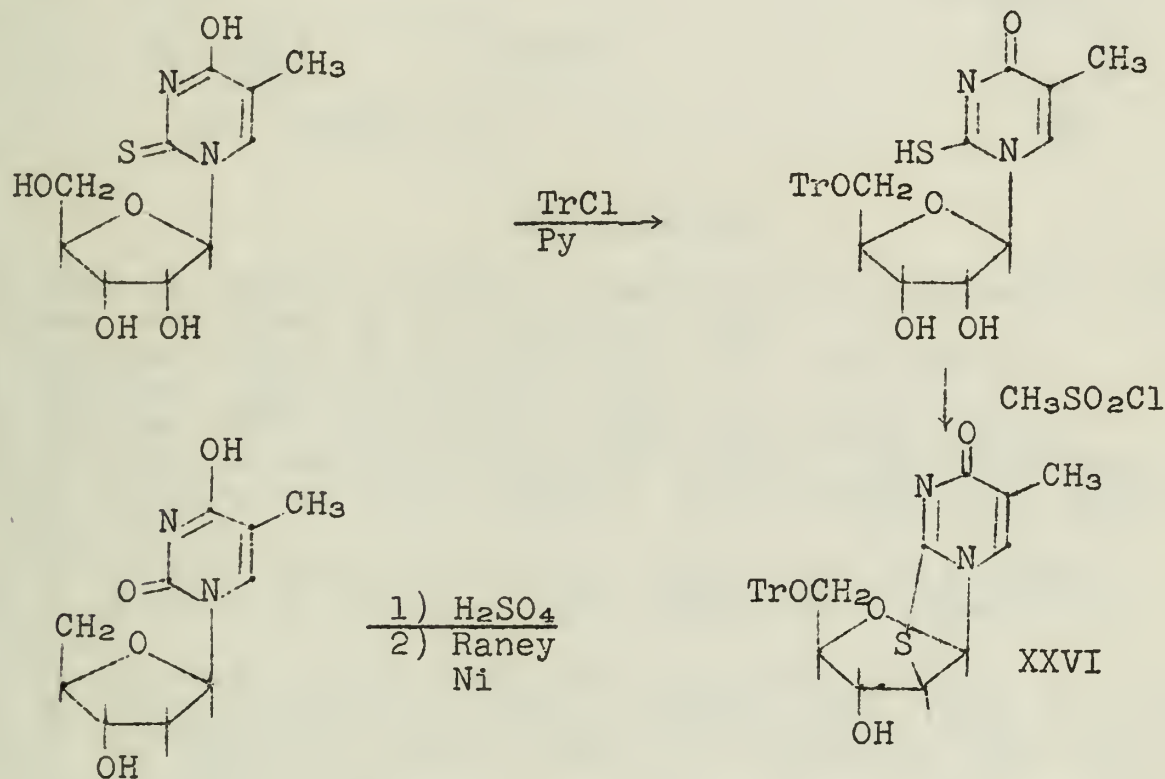


The 2'-tosyloxy group was replaced by iodide. Catalytic reduction followed by deacylation then gave 2'-deoxyuridine (XXV).





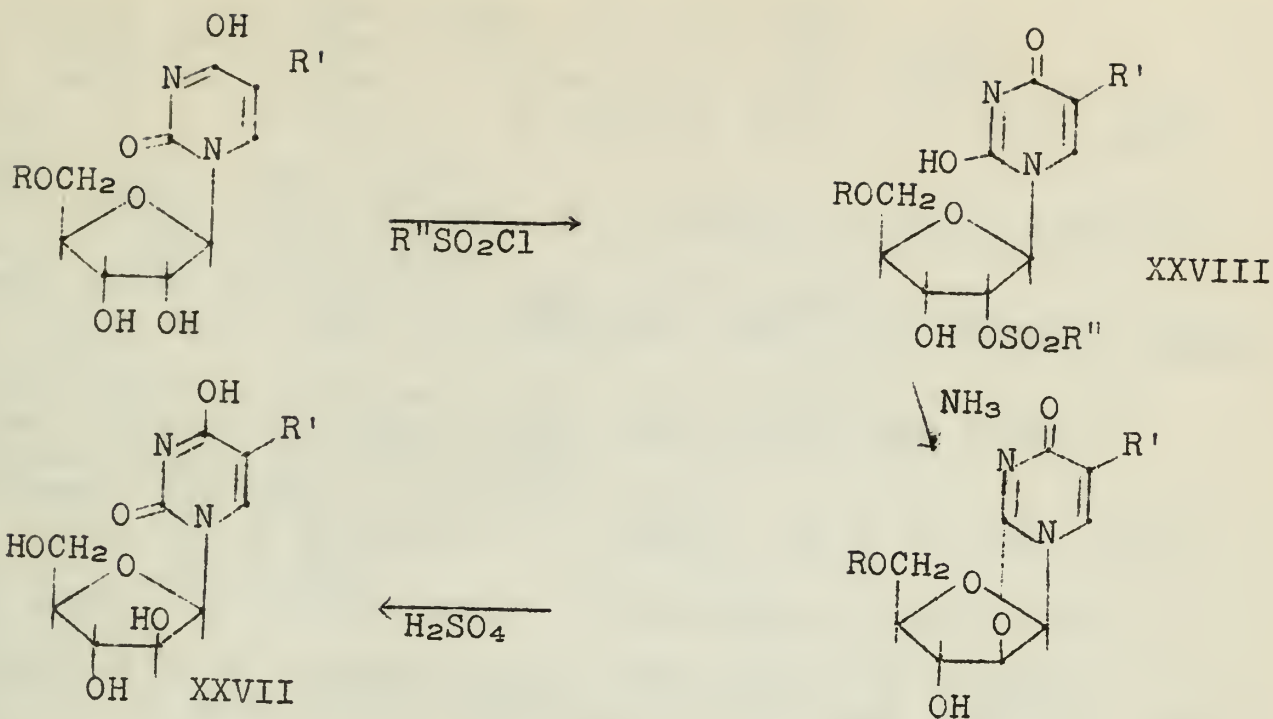
Shaw and Warrener used 5-methyl-2-thiouridine in the synthesis of thymidine (35). The 5'-position was blocked by means of a trityl group. Under the influence of methanesulfonyl chloride the 2-thiol function attacked the 2' position forming a cyclic compound, XXVI. This was converted to thymidine by removal of the trityl group and Raney nickel desulfurization.



Todd's group (33) and Fox, Yung, and Bendick (36) have used similar cyclizations in the 2-keto series to synthesize spongouridine (XXVII,  $\text{R}' = \text{H}$ ) and spongothymidine (XXVII,  $\text{R}' = \text{CH}_3$ ), two arabinose nucleosides which occur in sponges. In each case, treatment with a sulfonyl chloride -- p-toluenesulfonyl chloride in the uridine series, methanesulfonyl chloride in the thymidine series -- gave an isolable intermediate, XXVIII. Hydrolysis of the cyclic compound with sulfuric acid, in each case, gave inversion of configuration at the 2'-position.

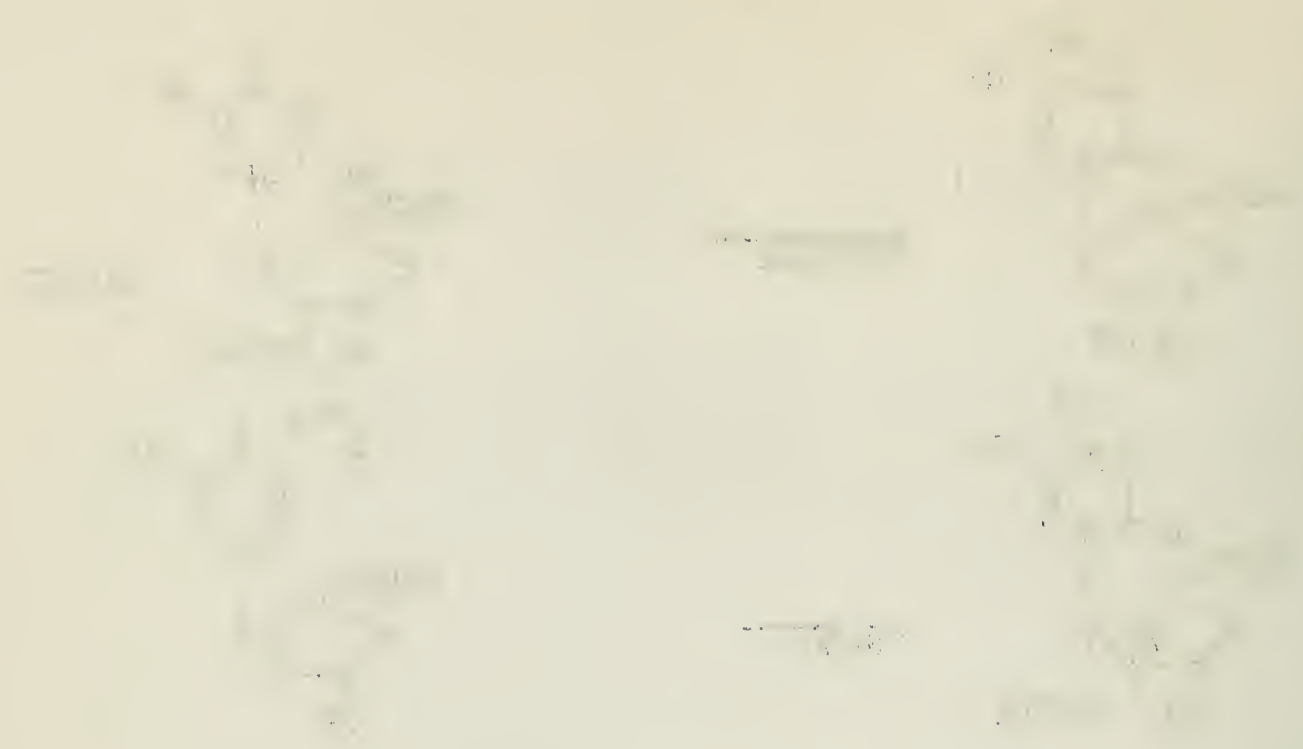






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PLANT SPECIES

1. *Platanus occidentalis* L. (Sycamore)  
2. *Acer rubrum* L. (Red Maple)  
3. *Fraxinus americana* L. (White Ash)  
4. *Quercus alba* L. (White Oak)  
5. *Corylus americana* B. (Hickory)  
6. *Juniperus communis* L. (Common Juniper)  
7. *Pinus strobus* L. (White Pine)  
8. *Larix laricina* (DuRoi) Koch (Norway Spruce)  
9. *Thuja occidentalis* L. (Eastern Arborvitae)  
10. *Abies balsamea* (Mill.) (Balsam Fir)  
11. *Picea canadensis* (Mill.) B.S.P. (White Pine)  
12. *Taxus canadensis* Mill. (Eastern White Pine)  
13. *Sequoia sempervirens* (D.D. Don) (Sequoiadendron giganteum) (Sequoia)  
14. *Metasequoia napewyanus* (Mill.) (Dawn Redwood)  
15. *Keteleeria davidiana* (H.B.K.) (Chinese Fir)  
16. *Podocarpus nathorstii* (Mill.) (Podocarpus)  
17. *Sciadopitys verticillata* (L.) (Japanese Cedar)  
18. *Chamaecyparis pisifera* (Mill.) (Japanese Cypress)  
19. *Juniperus horizontalis* (Mill.) (Creeping Juniper)  
20. *Juniperus communis* L. (Common Juniper)

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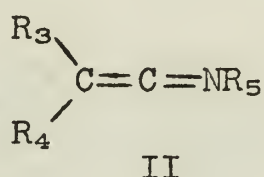
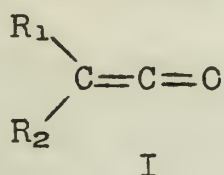


# THE NITROGEN ANALOGS OF KETENES: KETENIMINES

Reported by R. L. Talbott

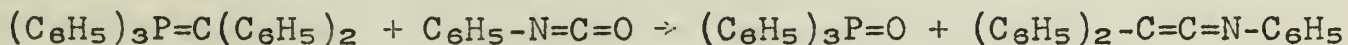
October 6, 1958

Ketene derivatives are well-known, useful compounds in organic chemistry. Analogous to the ketene compounds(I) are the ketenimines (II), in which the oxygen atom of a ketene has been replaced by a monosubstituted nitrogen atom. Several ketenimines are known, but their use in organic synthesis has until recently been given little attention. Many reactions of ketenimines are similar to those of the ketenes, although differences in reaction rate and in physical properties give the ketenimines a prominence of their own. The chemistry of ketenes has been reviewed elsewhere (1,2). This discussion will present the properties, preparations, and reactions of the ketenimines.



The properties of the ketenimines vary with the substituents in the molecule. Groups  $R_3$  and  $R_4$  may be aromatic or aliphatic; they may both be hydrogen; or they may be electron-attracting groups such as the methylsulfonyl or ethyl carboxylate radicals. Substituent  $R_5$  may be aromatic or aliphatic, but ketenimines with  $R_5 = \text{hydrogen}$  have not been isolated. The ketenimines are liquids or low-melting solids. When  $R_3$  or  $R_4$  is hydrogen, the compounds are unstable at room temperature and polymerize. Keten-ethylimine polymerizes so rapidly that its isolation in pure form has not yet been reported (3). In general, if  $R_3$  and  $R_4$  are aromatic, the ketenimines are stable and may be stored under nitrogen for long periods of time. The fifteen substituted ketenimines which have been reported have sharp, unpleasant, and irritating odors resembling those of aliphatic isocyanates (3). They are colorless, green, or yellow, depending on their substitution. Two ultraviolet maxima are generally observed. Diphenylketen-p-tolylimine, for example, has maxima at  $268.5 \text{ m}\mu$  ( $\log \epsilon = 4.48$ ) and at  $357 \text{ m}\mu$  ( $\log \epsilon = 3.14$ ) (4). The strong infrared absorption band near  $2000 \text{ cm}^{-1}$  has been assigned to stretching vibrations of the  $>C=C=N-$  grouping by analogy with the allene system (4,5,6).

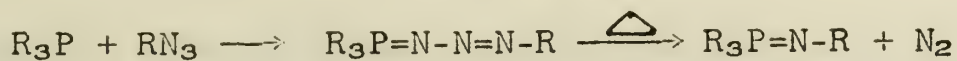
Preparation of ketenimines was first accomplished by heating a phosphinemethylene derivative with an isocyanate in benzene (7,8). After partial evaporation of the solvent the phosphine oxide was removed by filtration. Distillation of the filtrate under reduced pressure or recrystallization of the solute from petroleum ether afforded a purified ketenimine, which was characterized by acid catalyzed hydrolysis to a known amide.



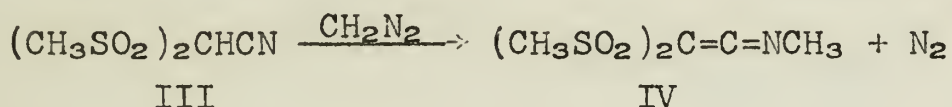
A more general and convenient method of ketenimine synthesis (3,9,10) is the reaction of a phosphinimide with a ketene in benzene under nitrogen. The phosphinimides may be obtained from reaction of phosphines with azides.



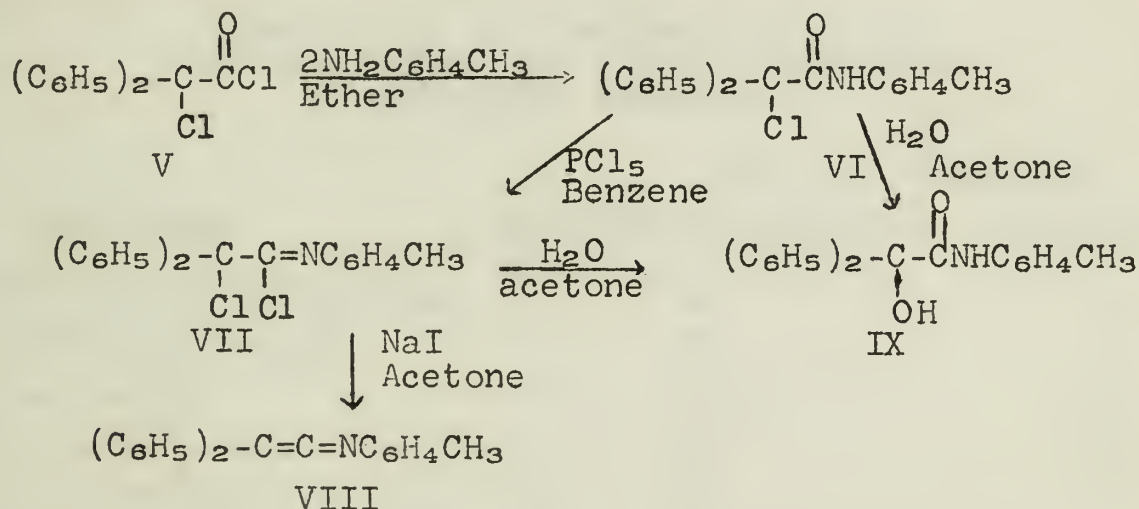




A third method of preparation was discovered when diazomethane was found to react with acetonitriles bearing two electron-attracting substituents, presumably when the acetonitriles were in the tautomeric form (11). bis-Methylsulfonylacetonitrile(III) condensed with diazomethane giving bis-methylsulfonylketen-methylimine(IV) in good yield. The structure of the product was shown by hydrolysis in boiling water to the corresponding amide. Acetonitriles bearing carboxylate ester substituents showed similar reactions.



Another synthesis of ketenimines results from the dechlorination of  $\alpha$ -chloroimidyl chlorides with sodium iodide in acetone (4). The starting material in the reaction scheme was prepared by action of phosphorus pentachloride on benzilic acid to give  $\alpha$ -chlorodiphenylacetyl chloride(V) in 87% yield (13). Since  $\alpha$ -chloro acid chlorides preferentially react with amines to give  $\alpha$ -chloro amides rather than  $\alpha$ -amino acid chlorides (14), this compound V was treated with two moles of *p*-toluidine in ether to afford the amide VI (81%). Treatment of VI with phosphorus pentachloride converted it to the  $\alpha$ -chloroimidyl chloride VII (87%), which was dechlorinated to diphenylketen-*p*-tolylimine(VIII) in 84% yield. The overall yield based on benzilic acid was 51%. Both VI and VII on hydrolysis in a water-acetone mixture yielded the amide IX.

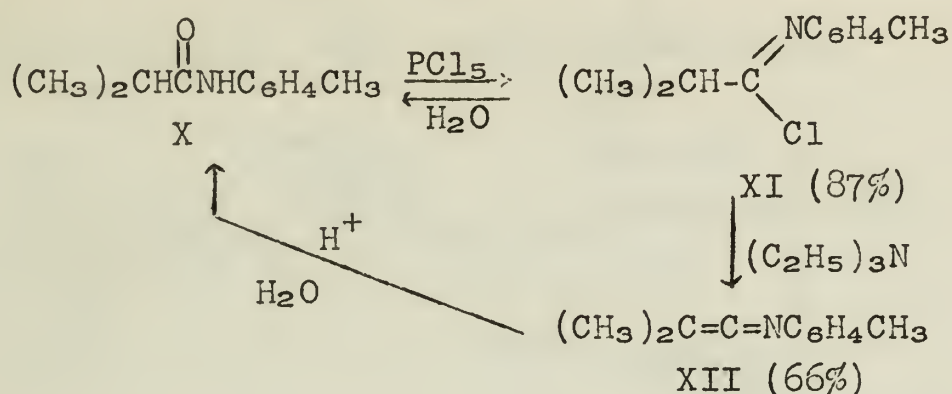


Certain ketenimines were not conveniently prepared by the dechlorination synthesis. A preferred method, analogous to a route of ketene preparation (18), was found to be dehydrochlorination of imidyl chlorides bearing a single  $\alpha$ -hydrogen atom (15). Early work had shown that the imidyl chlorides were unstable (16,17), but in a few instances they were isolated. Frequently they have been used as reactive intermediates without isolation. Action of triethylamine gave the desired ketenimines. The *p*-toluamide (X) of isobutyric acid was distilled with phosphorus pentachloride to afford the imidyl





chloride XI. Dimethylketen-p-tolylimine(XII) was obtained by treatment of XI with triethylamine. The imidyl chloride XI was hydrolyzed to starting material(X). The ketenimine structure for XII was also ascertained by hydrolysis to the amide X and by its infrared spectrum.



The two methods, dehydrochlorination with triethylamine and dechlorination with sodium iodide, complement each other. Their values in a particular preparation are determined by the stability of the corresponding  $\alpha$ -chloroimidyl chloride and the imidyl chloride intermediates. For the preparation of large amounts of ketenimines, dehydrochlorination appears to be the method of choice. For ketenimines which tend to dimerize easily dechlorination is more successful. As a structure proof several ketenimines were synthesized by both dechlorination and dehydrochlorination. Table I compares the percentage yields for the two reactions.

Table I

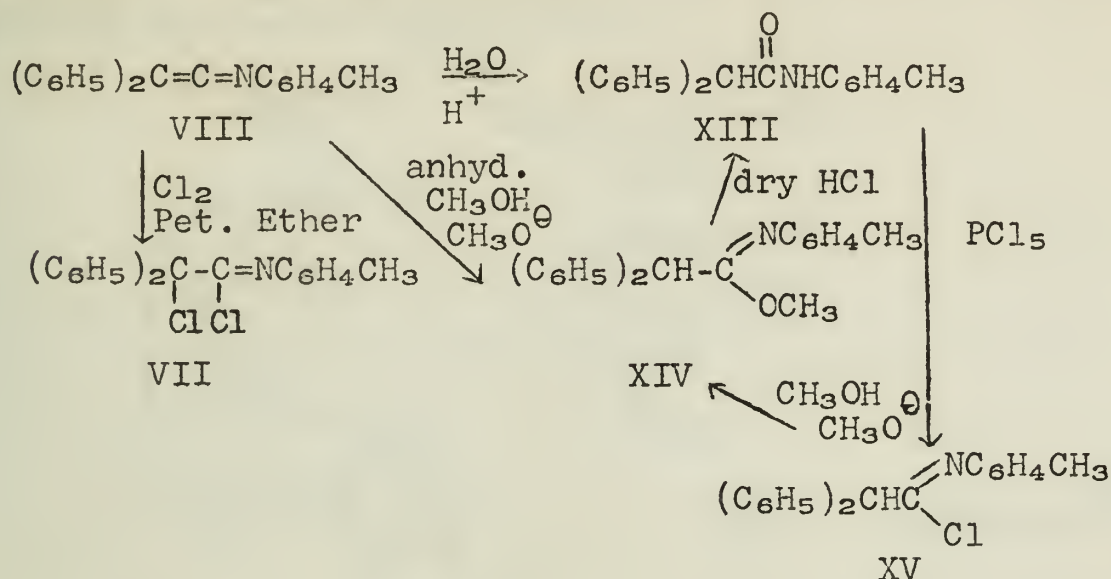
Comparison of Reaction Yields for  
Dehydrochlorination and Dechlorination  
in Ketenimine Preparations

<u>Ketenimine</u>	<u>Per Cent Yield by</u>	
	<u>Dehydrochlorination</u>	<u>Dechlorination</u>
$(\underline{n}\text{-C}_4\text{H}_9)(\text{C}_2\text{H}_5)\text{C}=\text{C}=\text{N}(\underline{n}\text{-C}_4\text{H}_9)$	57	...
$(\text{CH}_3)_2\text{C}=\text{C}=\text{NC}_6\text{H}_4\text{CH}_3(\underline{p})$	58	0
$(\text{C}_6\text{H}_5)_2\text{C}=\text{C}=\text{NCH}_3$	2.4	42
$(\text{C}_6\text{H}_5)_2\text{C}=\text{C}=\text{N}(\underline{n}\text{-C}_4\text{H}_9)$	69	63
$(\text{C}_6\text{H}_5)_2\text{C}=\text{C}=\text{NC}_6\text{H}_4\text{CH}_3(\underline{p})$	65	56

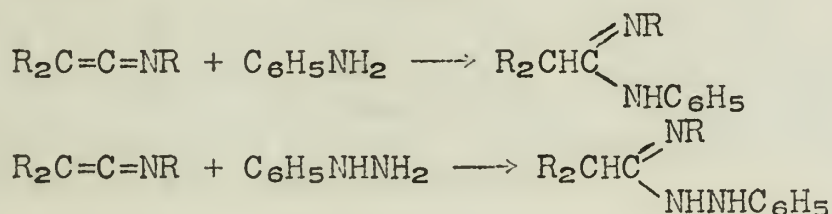
The slower reaction rates of ketenimine derivatives in comparison with those of ketenes is striking. In general, one observes that replacement of a carbonyl group by an imine group increases the reactivity of the molecule; Schiff bases, for example, are more reactive than aldehydes and ketones. This increased reactivity is not found in ketenimines. They are not autoxidizable except at elevated temperatures. With alcohol or water they are quite stable. Recrystallization of the unchanged solid ketenimines may be performed in ethanol, while heating in boiling water changes the ketenimines quite slowly (7). Acid catalysis is required for



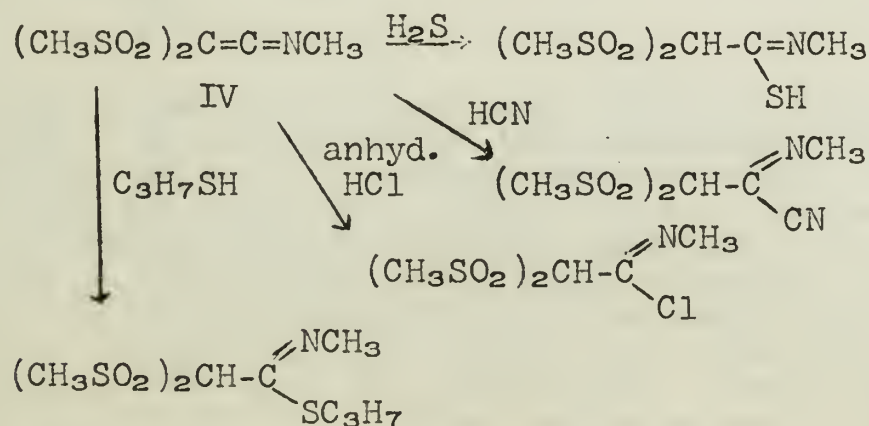
hydrolysis to the amides, and addition of base is necessary in alcoholysis reactions. Halogen adds to the olefinic double bond (4). The following reaction scheme depicts these reactions with diphenylketen-p-tolylimine (4).



The amide XIII was synthesized independently from the corresponding acid chloride and p-toluidine. All of these reactions proceeded smoothly in good yield. Furthermore, aniline and phenylhydrazine react with ketenimines (3).



Ketenimines bearing electron-attracting substituents are more reactive toward water and methanol (12). Reaction with amines is also more pronounced. In such substituted ketenimines addition at the olefinic double bond occurs, as illustrated by bis-methylsulfonylketen-methylimine (IV).

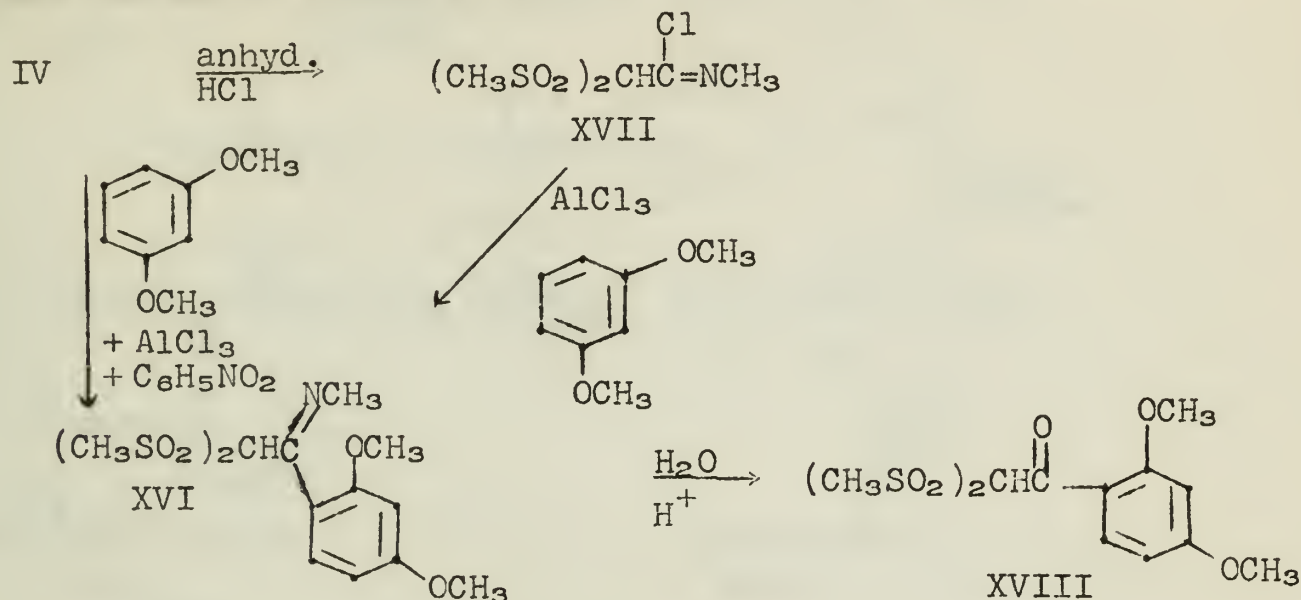


The ketenimines with electron-attracting substituents may be used in Friedel-Crafts type reactions (12). bis-Methylsulfonylketen-methylimine (IV), when treated with aluminum chloride and the

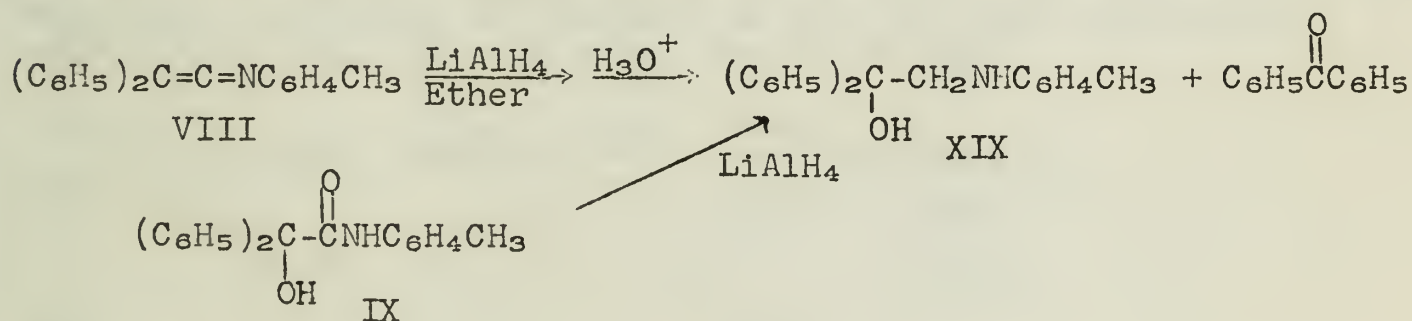




dimethyl ether of resorcinol in nitrobenzene, affords the imine XVI (39% yield). The same imine(XVI) was obtained by treating IV with anhydrous hydrogen chloride to give the imidyl chloride XVII, which also condensed with the dimethyl ether of resorcinol in the presence of aluminum chloride. Hydrolysis of the imine XVI provided the known ketone XVIII.



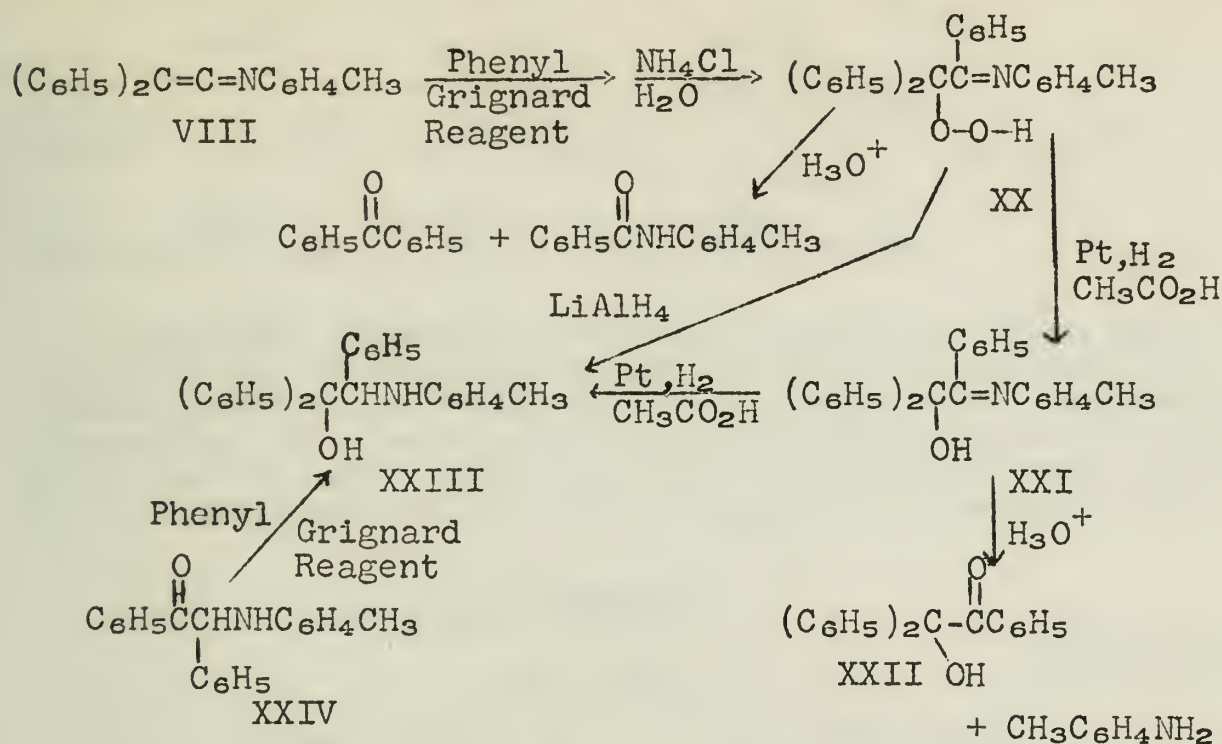
Attempts to characterize diphenylketen-p-tolylimine(VIII) by reduction with lithium aluminum hydride in ether, followed by isolation under acidic conditions, surprisingly gave the amino alcohol XIX in 60% yield (19). The alcohol was characterized by analysis and an acetate derivative. Another product isolated from the reaction mixture was benzophenone. Independent synthesis by reduction of the amide IX with lithium aluminum hydride substantiated the structure of the amino alcohol.



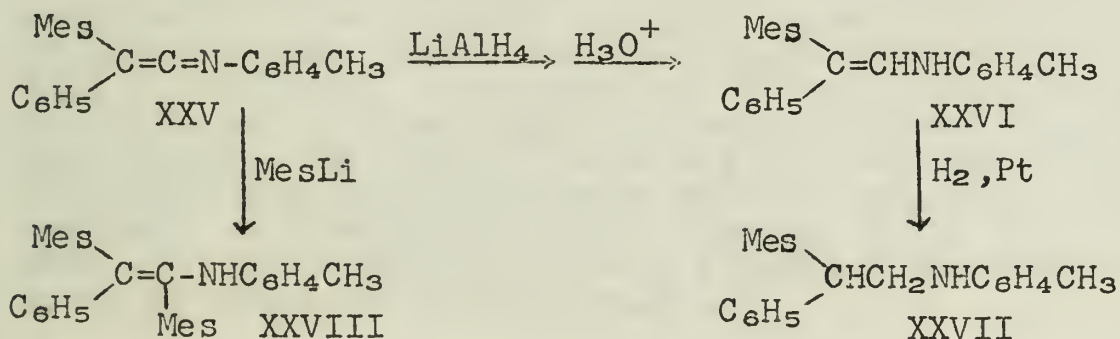
The course of amino alcohol formation has not been conclusively confirmed. Speculation that the products of the reaction may have formed through an intermediate hydroperoxide led to the synthesis and characterization of a similar hydroperoxide XX by treatment of diphenylketen-p-tolylimine(VIII) with the phenyl Grignard reagent, followed by hydrolysis of the organometallic complex in the presence of air. This hydroperoxide(XX) liberated iodine from an acidic potassium iodide solution. Catalytic reduction of XX gave the  $\alpha$ -hydroxy Schiff base XXI (92% yield). Hydrolysis of this Schiff base(XXI) afforded the known compounds,  $\alpha$ -hydroxy- $\alpha,\alpha$ -diphenylacetophenone(XXII) and p-toluidine. The hydroperoxide XX rearranged in acid solution to benzophenone and the p-toluidide of benzoic acid. Lithium aluminum hydride reduction of XX afforded the expected amino alcohol XXIII in 78% yield. The same amino alcohol(XXIII) was



obtained by catalytic reduction of the Schiff base XXI. The amino alcohol was also obtained by independent synthesis from the reaction of N-p-tolyldesylamine (XXIV) and the phenyl Grignard reagent.



An amino alcohol was not obtained by lithium aluminum hydride reduction of mesitylphenylketen-p-tolyimine (XXV). Rather, the vinylamine XXVI was isolated and was characterized by catalytic reduction to the known amine XXVII. Treatment of the ketenimine XXV with mesityllithium also provided a vinylamine XXVIII in good yield. The vinylamine XXVIII was extremely stable and was recovered unchanged from basic hydrogen peroxide solution after two days, and from acetic anhydride in pyridine as well as from concentrated hydrochloric acid after an equal amount of time.

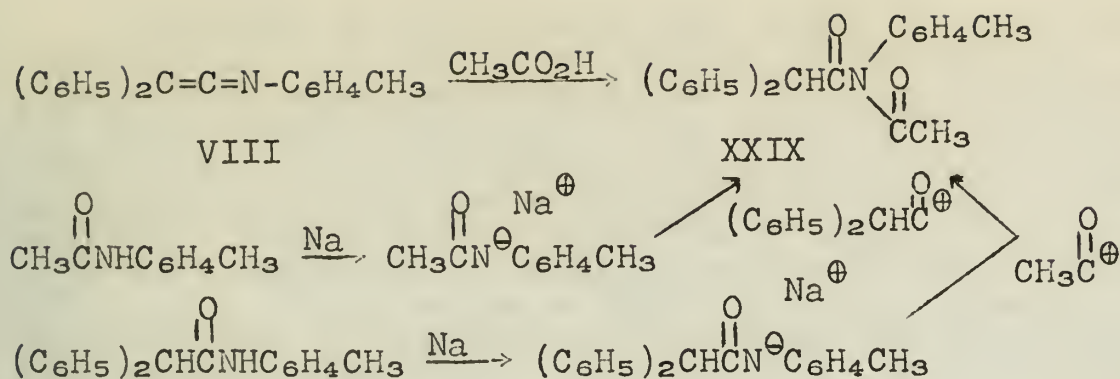


With carboxylic acids the ketenimines condensed readily in benzene solution to give the corresponding imides (20). Diphenylketen-p-tolyimine (VIII) reacted with acetic acid, benzoic acid, and diphenylacetic acid to give the imides in yields of 76, 87, and 80%, respectively. Synthesis of the imide XXIX by two other independent procedures excluded the possibility of O-acylation.

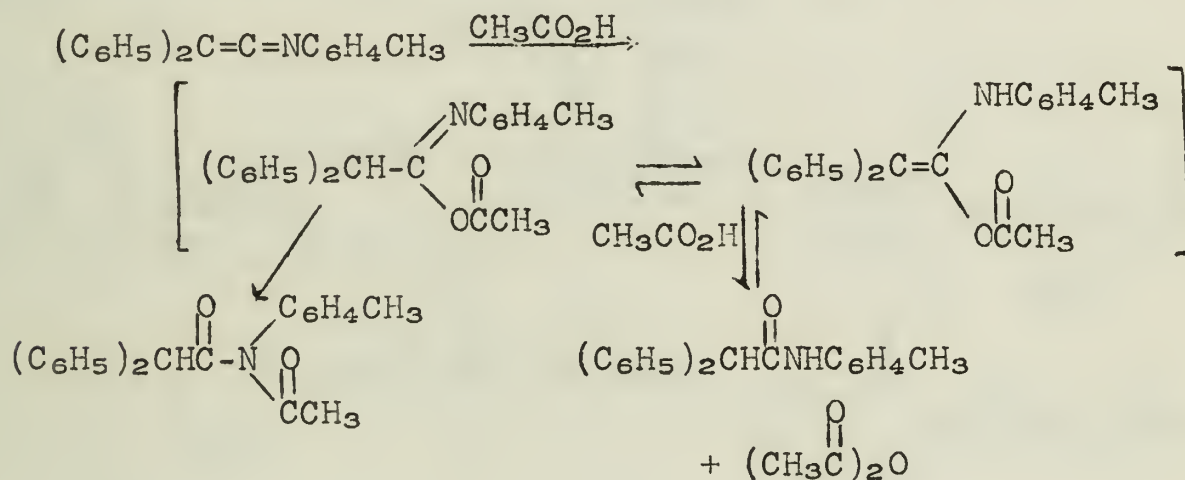




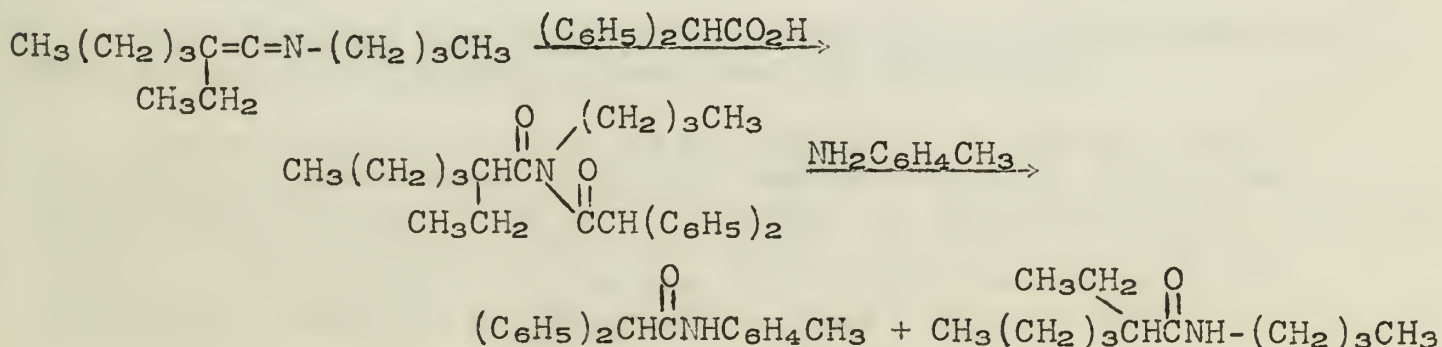




Anhydride formation and amide formation, which were observed in following the reaction by use of infrared spectra, indicated an intermediate which could not be isolated. The intermediate was presumed to be a more active acylating agent than the imide product, which was recovered unchanged when treated for nine hours in acetic acid. The course of the reaction may be represented in this manner:

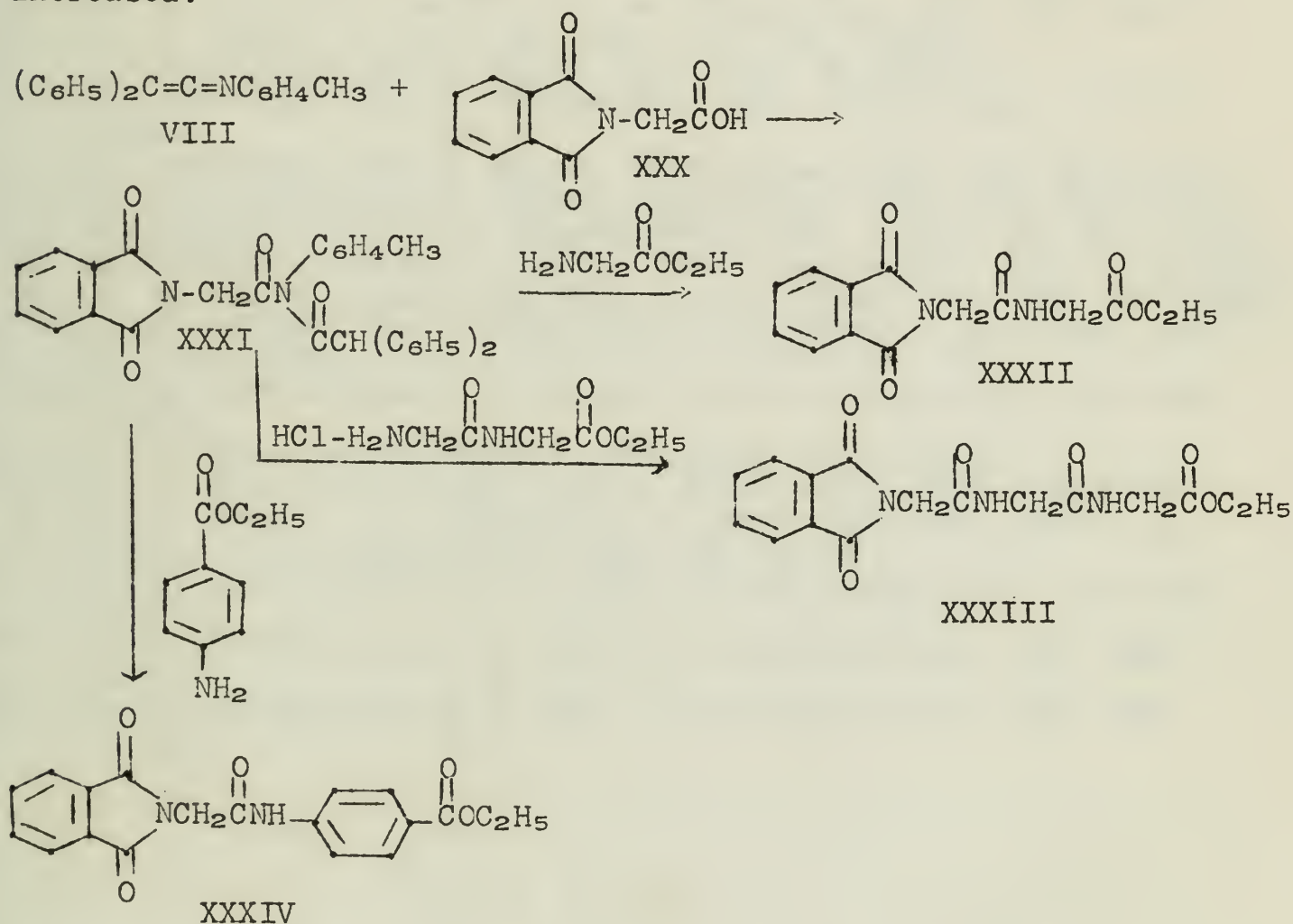


Although the imides did not acylate acetic acid at room temperature, they readily acylated alcohols and both aliphatic and aromatic amines. Base catalyzed alcoholysis of XXIX gave the amide XIII in 61% yield. Treatment of XXIX with one equivalent of *n*-butylamine in hexane gave the amide XIII and *N*-*n*-butylacetamide in good yield. The products obtained from several different imides indicated that both electronic effects and steric effects are important in determining which carbonyl group of the imide is attacked. An example of steric effects is hindrance of the carbonyl group by ethyl and *n*-butyl radicals.





Acylation of amino acids with imides obtained from ketenimines constitutes a new method of peptide synthesis (21). Phthaloylglycine(XXX) condensed with diphenylketen-p-tolyimine(VIII) to give the adduct XXXI in 92% yield. The imide XXXI is stable. Similar adducts from N-carbobenzoxylglycine, phthaloyl-β-alanine, and phthaloyl-DL-methionine were prepared in yields of 89, 76, and 60%, respectively. Acylation of glycine ethyl ester with XXXI gave the dipeptide, phthaloylglycylglycine ethyl ester(XXXII), in 70% yield. Condensation of XXXI with glycylglycine ethyl ester hydrochloride in triethylamine afforded the tripeptide, phthaloylglycylglycylglycine ethyl ester(XXXIII). The imide XXXI also reacted with an aromatic amino acid ester, ethyl p-aminobenzoate, yielding ethyl phthaloylglycyl-p-aminobenzoate(XXXIV). When the ketenimine, phthaloylglycine, and the amino acid ester were all placed in the reaction mixture simultaneously, the yields were increased.



When tyrosine was used in this method of peptide synthesis, protection of the phenolic group was not necessary.

Peptide synthesis with these imides as acylating agents is similar to various mixed anhydride methods as well as to the carbodiimide method. The use of imides is advantageous in that the active acylating agents for each amino acid can be isolated, purified, and stored. A disadvantage is the possibility of significant reaction at the wrong carbonyl of the imide.





An examination of the structure of a substituted ketenimine(II) reveals that where the two carbon substituents,  $R_3$  and  $R_4$ , are different, allene-type isomerism should be possible. To date no resolution has been reported.

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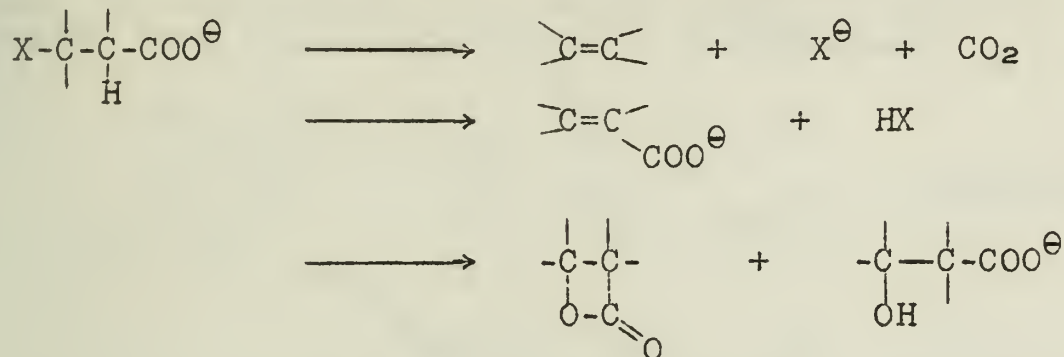


# REACTIONS OF SUBSTITUTED $\beta$ -HALOACIDS

Reported by C. L. Hwa

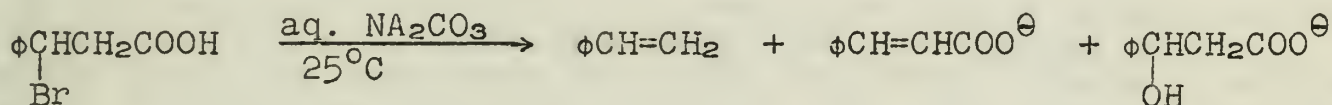
October 9, 1958

It has long been known that the salts of  $\beta$ -haloacids when dissolved in water undergo a reaction in which halide ion and carbon dioxide are lost. The reaction has associated with it several competing reactions which occur to a degree depending upon the structure of the acid, the basicity of solution, the temperature, and other factors.



The reaction involving the loss of halide ion and carbon dioxide has been called "dehalogenative decarboxylation".

The earliest extensive study on reactions of  $\beta$ -haloacids was made by Fittig (1). When  $\beta$ -bromocinnamic acid was treated with an aqueous sodium carbonate solution, styrene was obtained in 65% yield along with traces of  $\beta$ -hydroxyhydrocinnamic acid and cinnamic acid.



In similar manner,  $\beta$ -lactones were also obtained, invariably accompanied by the production of the hydroxyacids and olefins (2,3). Erlenmeyer (4) suggested that  $\beta$ -lactones were intermediates for the dehalogenative decarboxylation products, but Johansson and Hagman (5) later proved that this was not the case. Instead, a  $\beta$ -lactone is the precursor of the hydroxyacid.

Stereochemical studies on the mechanism of the decomposition reaction showed that the decarboxylation occurs through a trans elimination process (6,7). However, this was not widely accepted in the early days because of the fact that the salts of both erythro- and threo-dibromocinnamic acid in aqueous solution gave trans- $\beta$ -bromostyrene as the major product (8). More thorough investigation of the problem by Grovenstein and Lee (7) and by Cristol and Norris (6) showed that as the ionizing power of the solvent was decreased the reaction became more stereospecific. At  $80^{\circ}$ , the sodium salt of the erythro-dibromoacid gave in water a  $\beta$ -bromostyrene mixture (60% yield), 78% trans and 22% cis, and in absolute ethanol a mixture (27% yield), 13% trans and 86% cis (7). At reflux, the erythro-dibromoacid with excess sodium acetate in ethanol yielded a mixture (58%) of  $\beta$ -bromostyrenes, m.p.  $-17$  to  $-10^{\circ}$ , while the acid with excess sodium bicarbonate in acetone yielded a mixture (84%), m.p.  $-11^{\circ}$  to  $-8^{\circ}$ , richer in cis- $\beta$ -bromostyrene (pure cis m.p.  $-7$  to  $-6^{\circ}$ ) (6).

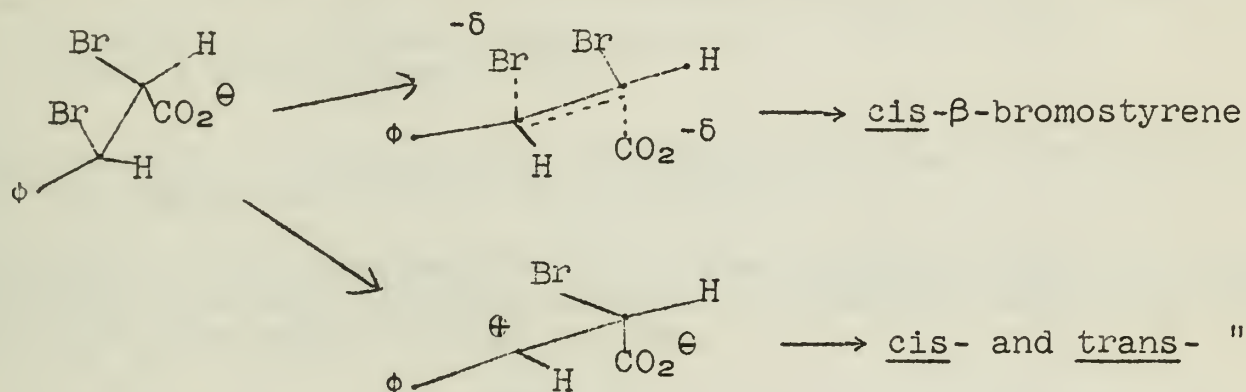






Melting point determinations were used by Cristol and Norris in making rough assignments of the proportions of the geometric isomers, while Grovenstein and Lee employed infrared analysis for their assignments, based upon the striking differences of the spectra of cis- and trans- $\beta$ -bromostyrene in the 10-14  $\mu$  region. The cis- $\beta$ -bromostyrene was found not to isomerize under the reaction conditions (6).

Cristol and Norris also showed that, in sodium acetate and absolute ethanol, erythro- $p$ -nitrodibromocinnamic acid gave pure cis- $\beta$ -bromo- $p$ -nitrostyrene (13). A dual mechanism has been proposed to account for these facts: a concerted trans elimination and a two-step mechanism involving a zwitterion as intermediate.



A dehydrohalogenation reaction occurs, in general, in relatively strong basic solution and is suppressed almost completely in weakly basic solution at near room temperature (9).

By following the appearance of bromide ion in the kinetic study of the decomposition of sodium  $\beta$ -bromobutyrate in aqueous solution, Johansson found two concurrent reactions:  $\beta$ -lactone formation and the formation of propylene and carbon dioxide (10). The rate of formation of bromide ion was approximately first order in  $\beta$ -bromobutyrate anion. Later work is in agreement with this finding (5,11-13) except that Vaughan (13) went further to find that the rate of bromide ion formation is first order in  $\beta$ -haloacid anion in moderately basic medium, and at pH greater than 8.5 the rate is also first order in the hydroxyl ion concentration.

Some of the kinetic studies involved the effect of substituents on the  $\beta$ -haloacids on the competition between dehalogenative decarboxylation and  $\beta$ -lactone formation (12,14). Since both the decarboxylation and lactone formation are first order reactions in carboxylic acid anion, the over-all rate when the two occur together is also first order. When the relative amounts of  $\beta$ -lactone (or hydroxyacid) and olefin (or carbon dioxide) are known, the rate constant can be partitioned into a constant for lactone formation,  $K_L$ , and one for olefin formation,  $K_O$ . The logarithm of  $K_O/K_L$  is proportional to the difference in the free energy of activation of the two competing processes.

The effects of the  $\beta$ -substituents on the rate (16) are shown in Table I, the  $K_O/K_L$  for  $\beta$ -bromopropionic acid being assumed to be  $10^{-2}$  (15). When the  $\beta$ -carbon is tertiary, decarboxylation is accelerated over lactonization. Since the reactions described above were run in neutral aqueous solutions (no comparable data are available when the reactions are run in non-aqueous solvents), the larger effect of



TABLE I

	R <sub>1</sub>	H	Me	n-Pr	Me
	R <sub>2</sub>	H	H	H	Me
$\begin{array}{c} R_1 \\   \\ BrC-CH_2COO^\ominus \\   \\ R_2 \end{array}$	Relative rate for $\beta$ -lactone formation	1*	4.3	10	$10^4$
	Dehalogenative decarboxylation	1*	100	--	$3 \times 10^6$
	$K_O/K_L$	0.01	0.2	(2**)	3.5

(\* Different relative rate scales)  
(\*\*For  $\beta$ -bromocinnamic acid)

the substituents on decarboxylation is presumably due to the stabilization of the carbonium ion at the  $\beta$ -carbon.

The effect of the  $\alpha$ -substituents on the relative rates of decomposition of  $\beta$ -haloacids is shown in Table II; however, no values for the ratio  $K_O/K_L$  are given in this series.

TABLE II

	R <sub>1</sub>	H	Et	Me
	R <sub>2</sub>	H	H	Me
$\begin{array}{c} R_1 \\   \\ BrCH_2-C-COO^\ominus \\   \\ R_2 \end{array}$	Relative rate for: $\beta$ -lactone formation	1*	8	90
	Dehalogenative decarboxylation	1*	50	200

(\*Different relative rate scales)

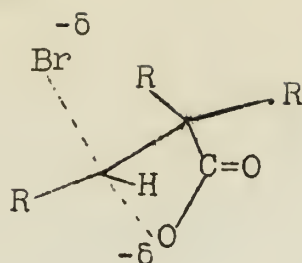
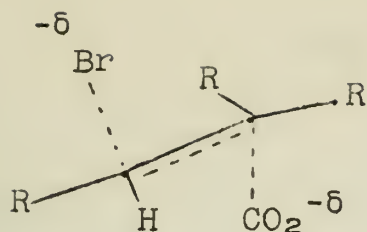
The accelerating effect of the alkyl groups is probably due to the relief of steric strain in both decarboxylation and lactonization, and the effect is smaller on the latter. The situation is more complicated when the  $\alpha$ -carbon is substituted and the  $\beta$ -carbon is not primary.

When  $C_\beta$  is primary and  $C_\alpha$  carries only a single halogen or phenyl, only slight olefin formation is detected (5,15); thus  $K_O/K_L < 0.01$ . This ratio is increased to 0.4 (factor of 40) when  $C_\alpha$  carries two halogens or phenyls. If, however,  $C_\beta$  is not primary and  $C_\alpha$  is disubstituted, as in  $\alpha,\alpha,\beta$ -tribromohydrocinnamic acid,  $K_O/K_L$  is raised from 2.5 (for  $\beta$ -bromohydrocinnamic acid) to 12.5 (factor of 5). In the latter case, the resulting olefin and lactone must pass through a transition state in which vicinal groups interact sterically. It is not clear why the lactonization is preferred over olefin formation under such circumstances.









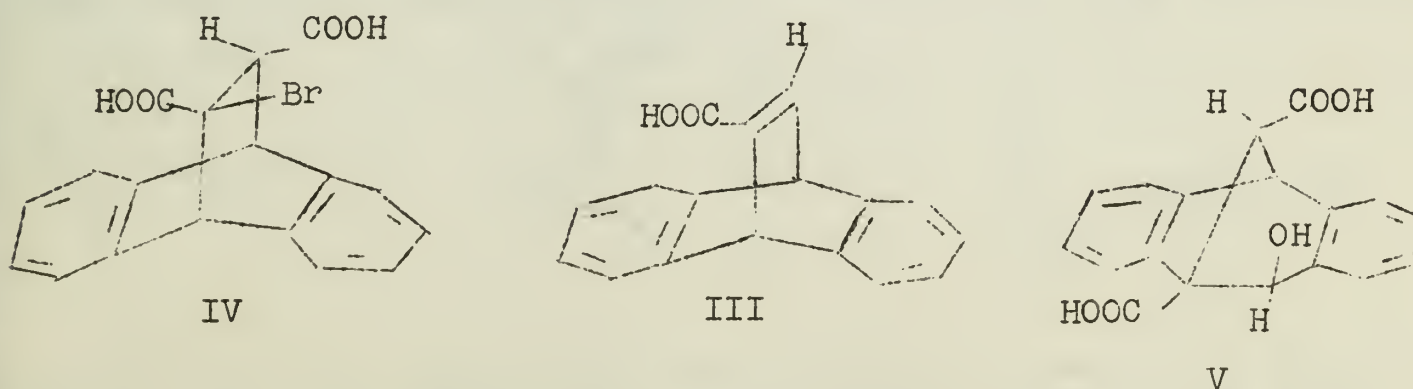
Walden inversion is also observed in the substitution reactions (14,19,20). In either acid or basic medium, inverted hydroxyacids were obtained, but there was no inversion in neutral medium. This confirms that the lactone formation is an intermediate to hydroxyacid, and the inversion is dependent on the hydroxyl ion concentration during the hydrolysis of lactone. Bartlett and Rylander have made use of the participation of the  $\beta$ -aroyl group in the study of inversion (20).

In recent years, some extensive studies have been made on the  $\beta$ -haloacids in which the rotation along the  $C_\alpha-C_\beta$  bond is restricted. The system studied is the 2-bromodibenzobicyclo[2.2.2]octadiene-2,3-dicarboxylic acid (21-27). The striking features of this system are the rigid hindered structure, participation of the  $\beta$ -carboxyl group, and the effect of the geometry at the reaction site on the course of reaction.

Bartlett and Scott found that 2-bromodibenzobicyclo[2.2.2]octadiene-2,3-dicarboxylic acid anhydride (I), when dissolved in alkali gave the inverted hydroxy-trans-dicarboxylic acid II (21).



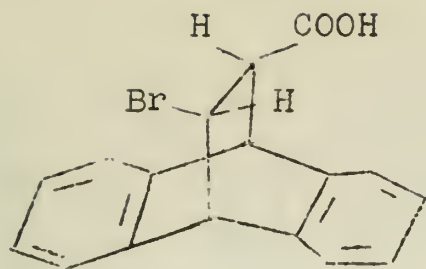
In 1952, Vaughan and Milton obtained the same inverted hydroxyacid, but they also isolated an unsaturated acid III from the reaction product (22). When the bromo-trans-diacid analogue IV was used as the starting material, they obtained a rearrangement product V and the same unsaturated acid III. Because of the geometry of the reaction site of IV, a  $\beta$ -lactone intermediate is not possible, hence no corresponding inverted hydroxyacid was found.



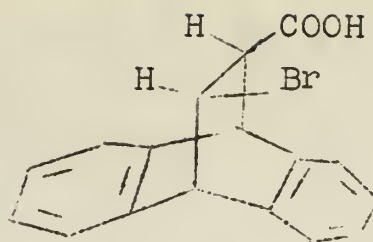


The first of these is the fact that the bird is not a true bird, but a member of the class of animals known as the "Aves". The second is that it is not a true bird, but a member of the class of animals known as the "Aves". The third is that it is not a true bird, but a member of the class of animals known as the "Aves".

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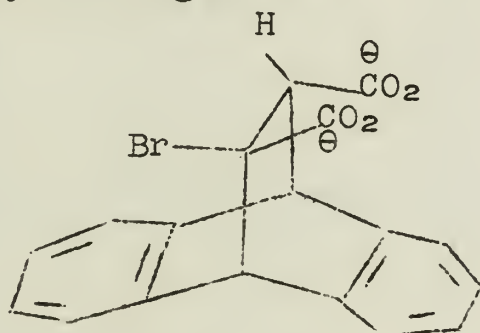
VI



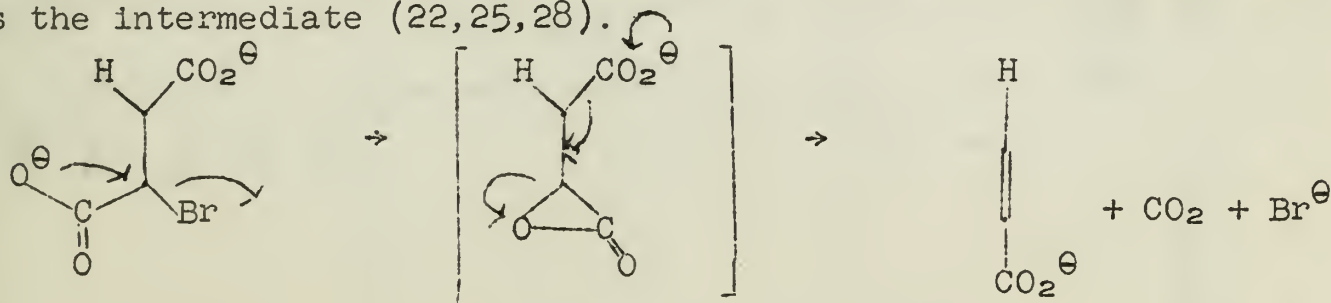
VII

The relative ratios of the products obtained from both the mono- and di-carboxylic acids under different conditions are summarized in Table III. Although the general picture is somewhat complicated by the existence of rearrangement products, some conclusions can be reached in correlating the geometry of the structure and the data obtained.

The striking characteristics of the reaction of trans-bromoacid VI with excess alkali are the complete absence of a product from  $\beta$ -lactone formation and the negligible occurrence of dehalogenative decarboxylation, whereas these two reactions accounted for the entire product when the stereochemically similar dibasic acid IV was treated under the same conditions. In the latter, no dehydrohalogenation was observed. These facts may be understood by looking at the geometry of the system in which the mutual repulsion of the two carboxylate groups provides a structural situation resulting in a conformation more approximating that required for  $\beta$ -lactone and decarboxylation and less favorable for cis-dehydrohalogenation.



The formation of the unsaturated acid III from I is attributed to trans-elimination of bromide ion and carbon dioxide, whereas that from IV is obviously the result of a different reaction path. A possible explanation is the two-step mechanism involving the  $\alpha$ -lactone as the intermediate (22,25,28).



Preference for trans-dehydrohalogenation is observed in the reaction of the cis-bromoacid VII and this is in contrast with known cis-elimination in similar systems (29). In this case, the repulsion

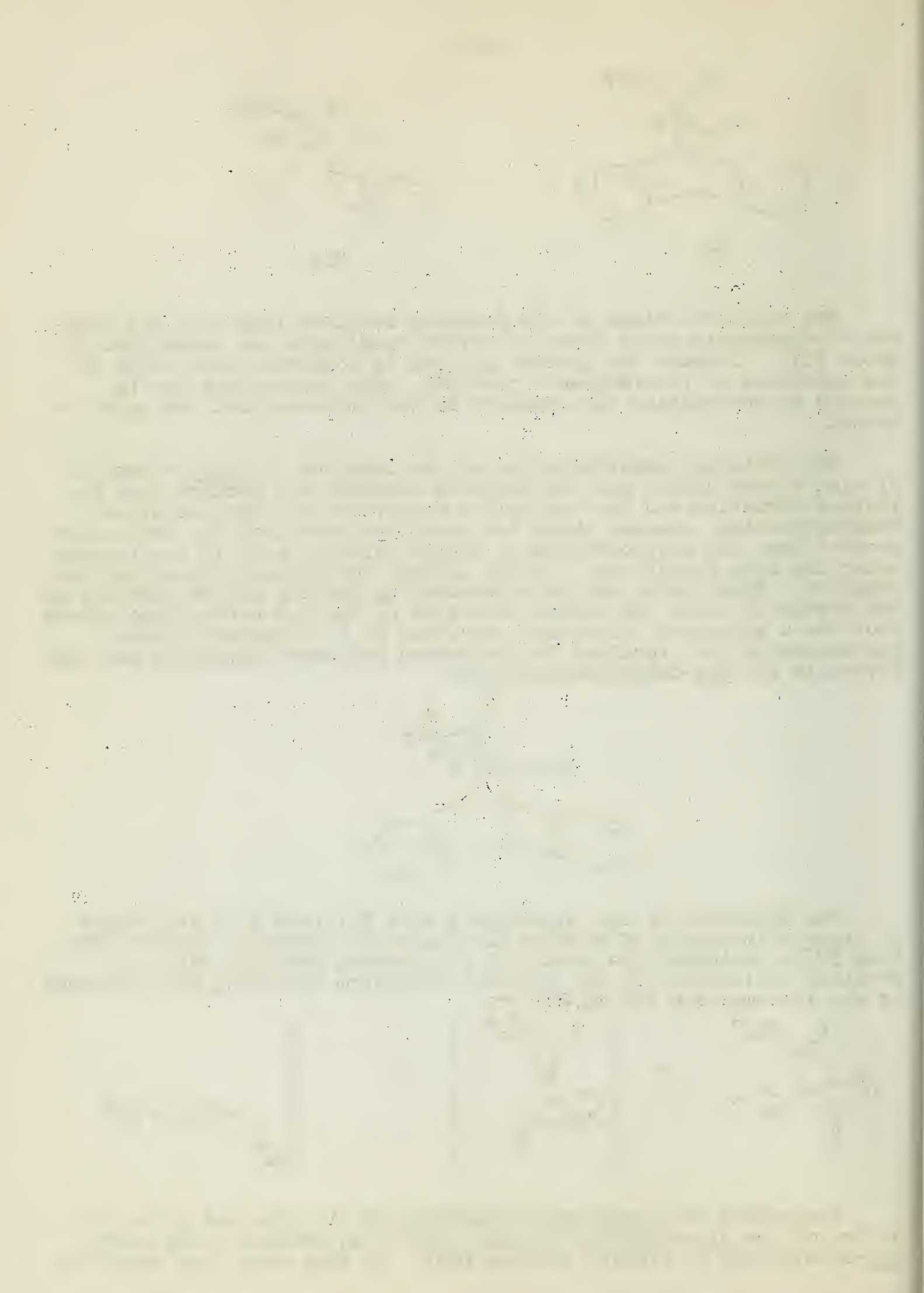
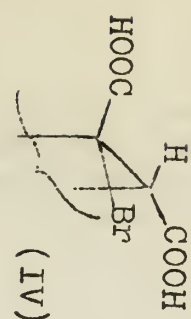
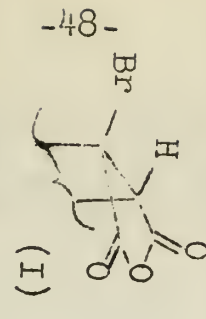
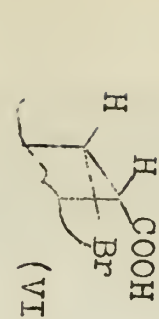
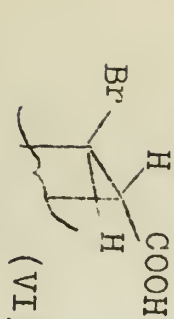
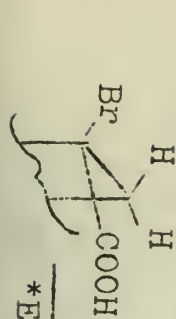


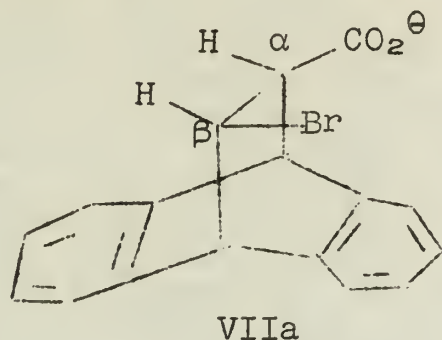


TABLE III  
Summary of Reaction Data

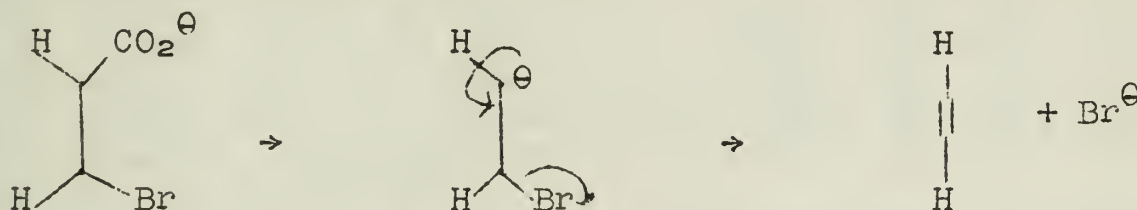
<u>Reactant</u>	<u>Reagent</u>	<u>Lactoni-</u> <u>zation</u>	<u>Dehalogenative</u> <u>decarboxylation</u>		<u>Dehydrohalogenation</u>		<u>Rearrangement</u>
			<u>cis</u>	<u>trans</u>	<u>cis</u>	<u>trans</u>	
 (IV)	NaHCO <sub>3</sub> -acetone NaOH AgNO <sub>3</sub>		11 3 1				1 2 5
 (I)	NaOH NaHCO <sub>3</sub> -acetone AgNO <sub>3</sub> Ag <sub>2</sub> O	3 2 8 14		2 1 1			1 0.1 (?)
 (VII)	NaOH NaHCO <sub>3</sub> -acetone AgNO <sub>3</sub>		5 24 19			95 76	
 (VI)	NaOH NaHCO <sub>3</sub> -acetone AgNO <sub>3</sub>			4	45 32		55 64 100*
 *Epimeric products	NaOH AgNO <sub>3</sub>						100 100*



of the bromine and carboxylate anion (VIIa) causes the  $\alpha$ -hydrogen,  $C_\alpha$ ,  $C_\beta$  and bromine to be close enough to coplanarity to permit normal trans-dehydrohalogenation. Although the same geometry prevails in IV, the absence of the trans-dehydrohalogenation is due to the fact that IV is also an  $\alpha$ -haloacid.

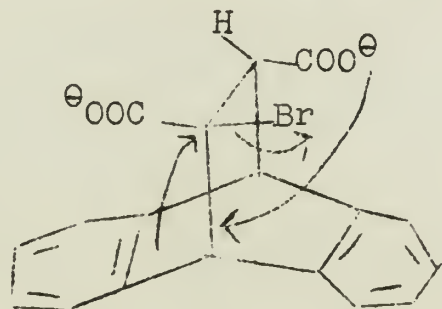


The cis-dehalogenative decarboxylation which is obtained in IV has already been explained by the participation of the neighboring carboxylate group in forming an  $\alpha$ -lactone intermediate, but in the absence of this neighboring carboxylate group, VII still gave cis-decarboxylation products. This fact cannot be explained by the repulsion of the bromine and the carboxylate group, used to account for the trans-dehydrohalogenation. The zwitterion mechanism is also inapplicable because it should not be operative in acetone solution (6). Vaughan and Schoenthaler (27) proposed a two-step mechanism reminiscent of Cristol's cis-dehydrohalogenation (29). They argued that although



ordinarily this is considered to require too much energy to compete successfully with the other reactions, in the present system it is competing only with dehydrohalogenation which does not have an ideal geometry.

The mechanism of rearrangement in this system is pictured as concerted:



In the base-induced rearrangement, there is nothing significant beyond ordinary solvation in the way of assisting removal of bromine. Thus, where geometry of the system permits, other reactions can compete quite successfully--even to complete exclusion of rearrangement. In case of electrophilic attack (as silver nitrate) on bromine, the carbonium ion character would favor rearrangement.





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# NEIGHBORING GROUP PARTICIPATION IN ADDITION REACTIONS

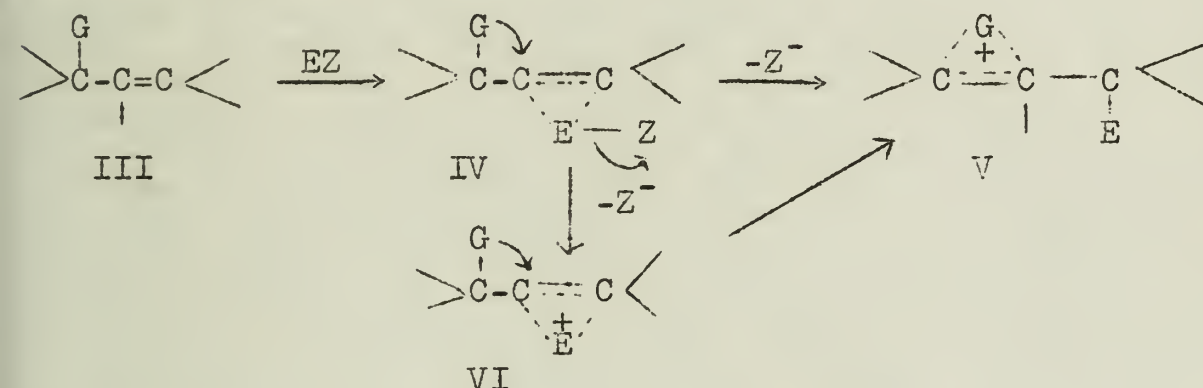
Reported by W. J. Koehl, Jr.

October 13, 1958

The literature of organic chemistry contains numerous examples of replacement reactions in which a group on an adjacent atom participates. This phenomenon may be formulated as shown by I and II where G is the



neighboring group (1). Through the formation of the cyclic intermediate II, the neighboring group assists in the toleration of the electron-deficiency created by the ionization of the group Y. Neighboring groups may also participate in addition reactions in which the electron-deficiency is created by the attack of an electrophilic reagent on the olefinic double bond (2). This situation may be represented as follows (1).



The bridged structure V may be formed directly from the olefin-EZ complex IV or by way of the bridged ion VI. A classical analogue of this latter path may be found in the following rearrangement (8).



The question of neighboring group participation in replacement reactions and rearrangements up to 1950 has been reviewed by Winstein (3). This seminar will be limited to the consideration of neighboring group participation in addition reactions.

The effectiveness of a neighboring group in determining the products of a reaction is dependent upon the nucleophilic strength of the group relative to that of the solvent and other solutes.

The influence of a neighboring group in an addition reaction is often seen in the formation of cyclic products. One of the classic examples is the bromination of *o*-allylphenol in which Adams and Rindfusz (4) obtained a mixture of 2-methylcoumarane and three of its brominated derivatives but none of the expected dibromide. In the mercuriation of the same compound, the corresponding 2-mercurimethyl-

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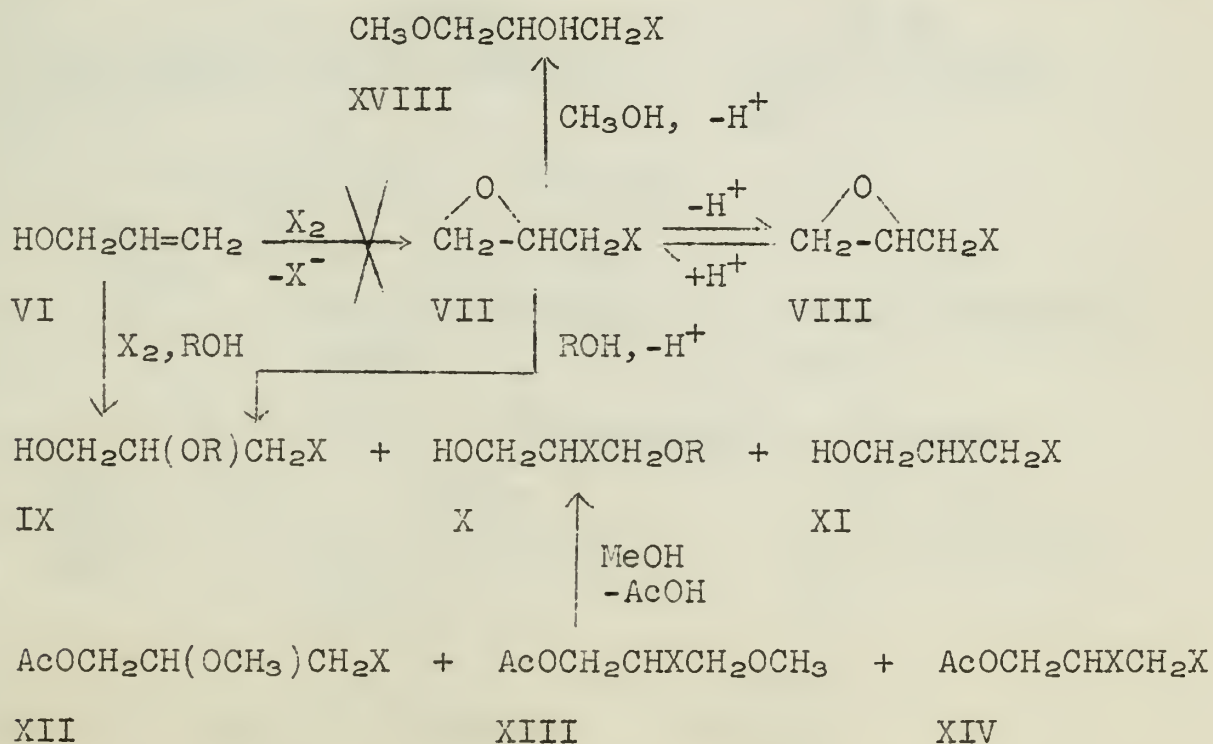
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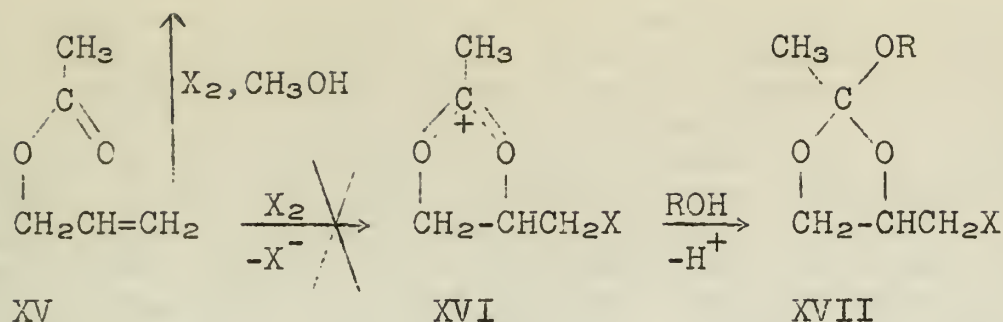


coumaranes were obtained (5). The normal addition product has been suggested as an intermediate, but there is no evidence of its formation in the reaction. 2-Chloromercurimethyltetrahydrofuran and 2-methyl-5-chloromercurimethyltetrahydrofuran were obtained by Nesmeyanov and Lutsenko (6) from 1-penten-4-ol and 1-hexen-4-ol in a similar reaction. In the majority of cases it is not clear whether the heterocyclic compound is the primary reaction product or whether it is formed from a normal addition product (1). However, Tarbell and Bartlett (7) obtained halo- $\beta$ -lactones in the chlorination and bromination of 2,3-dimethylmaleic and fumaric acids in aqueous solution. Neither the halohydrins nor the one dihaloacid known at that time--one of the isomers of 2,3-dichloro-2,3-dimethylsuccinic acid--could be converted to the lactone; therefore, the normal addition product could not have been an intermediate. This seems to be a clear case in which a neighboring carboxyl group has participated in an addition reaction.

Winstein and Goodman (1) have studied the halogenation of allyl alcohol and allyl acetate. If the hydroxyl group participates in the addition of halogens to the double bond of allyl alcohol (VI), the epihalohydrin VIII should be expected among the products (1). Addition of bromine and chlorine to aqueous solutions of allyl alcohol in the presence of sodium bicarbonate gave the dihalides XI in 26 and 3% yields. In neither case was there any evidence of the formation of an epihalohydrin VIII. Furthermore, no epihalohydrin was obtained in the bromination of allyl alcohol in an aqueous suspension of silver oxide. The addition of chlorine to allyl alcohol in anhydrous methanol in the presence of silver acetate gave less than 1% of a product which may have been the epichlorohydrin VIII and 64% of a mixture of the chloroethers IX and X in which IX ( $R = CH_3$ ,  $X = Cl$ ) predominated. When N-bromosuccinimide was used as a positive bromine source in methanol, allyl alcohol was converted in 73% yield to a mixture which was predominantly IX ( $R = CH_3$ ,  $X = Br$ ). The acid-catalyzed opening of the epihalohydrin VIII in methanol gives largely the secondary alcohol XVIII, but a small quantity of the primary alcohol IX is also formed.

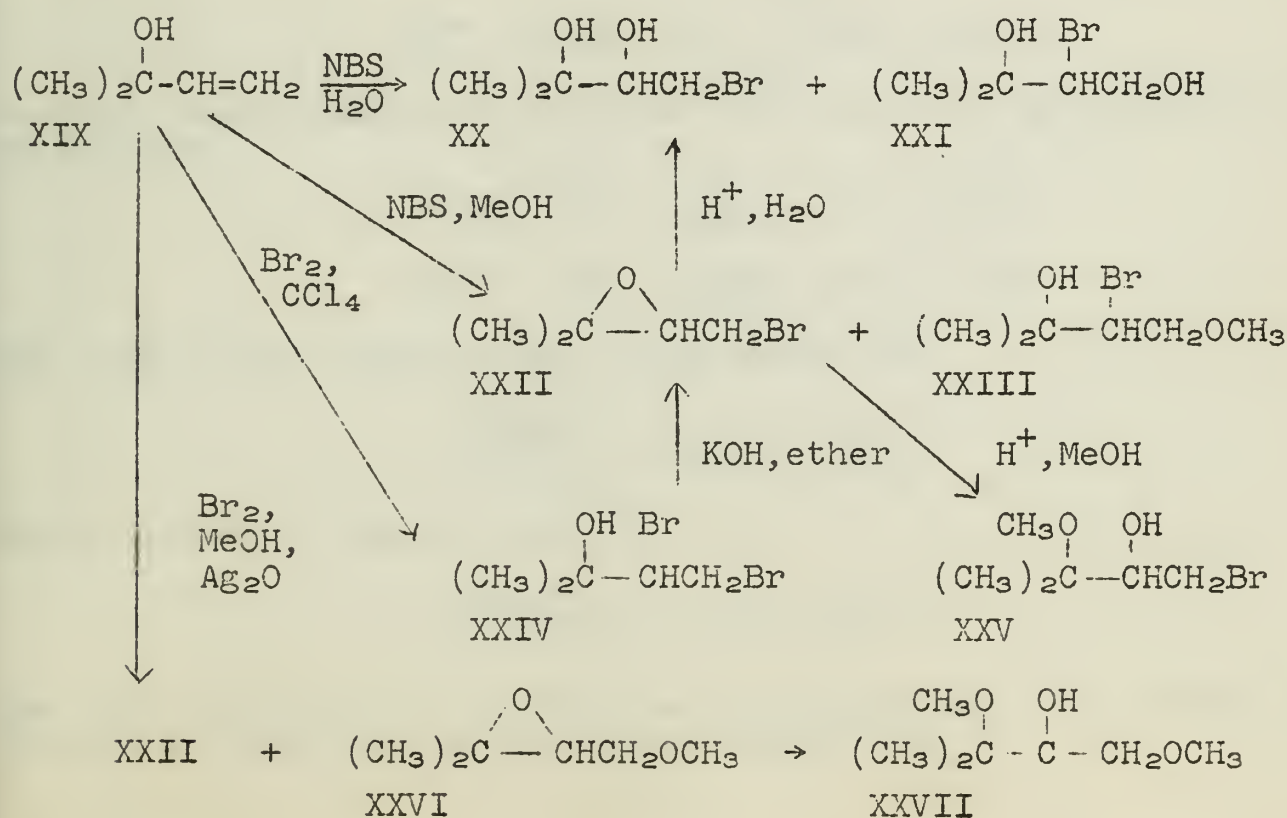






Participation of the acetoxy group in addition reactions on allyl acetate (XV) would be expected to produce an intermediate XVI, which in anhydrous alcohol would be converted to the orthoester XVII (1). The formation of such an orthoester, the ethylorthoacetate of cis-1,2-cyclohexanediol, has been observed (9) in the solvolysis of trans-2-acetoxycyclohexyl p-toluenesulfonate. The addition of chlorine to allyl acetate in methanol in the presence of silver acetate yielded a mixture of chloroethers XII and XIII which could be transesterified to a mixture of IX and X, but there was no evidence of an orthoester. Similar results were obtained in bromination.

There should be a correlation between the incidence of neighboring group participation in addition reactions and the size of the driving force due to the participation of the same groups in substitution reactions (1). Methyl groups on the carbon holding the participating group--the  $\beta$ -carbon of structure I--increase the driving force due to the participation of that group (10). Therefore, the participation of the tertiary hydroxyl group of 1,1-dimethylallyl alcohol in addition reactions would be more likely than that of allyl alcohol. In studying the bromination of this alcohol, Winstein and Goodman (11) eliminated the competition between the neighboring group and bromide ion for nucleophilic attack on the carbon atom in question by using N-bromosuccinimide or bromine in the presence of silver oxide as the positive bromine source.





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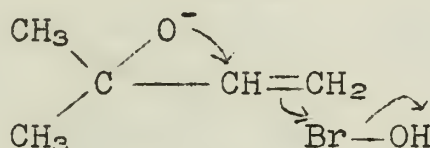
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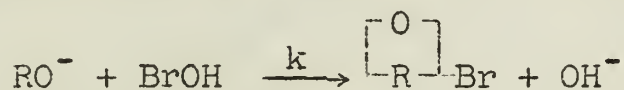
The addition of bromine to 1,1-dimethylallyl alcohol (XIX) in methanol containing silver oxide gave two epoxides, XXII and XXVI. A control showed that XXII is not easily converted to XXVI under the reaction conditions and is probably formed by silver oxide dehydrohalogenation of the bromohydrin XXIII, which can be isolated as the main product in the absence of silver oxide. The reaction of N-bromosuccinimide with 1,1-dimethylallyl alcohol in anhydrous methanol was relatively slow; however, the epibromohydrin XXII and the bromohydrin XXIII were formed in 8 and 46% yields. On treatment with N-bromosuccinimide in water, 1,1-dimethylallyl alcohol was converted to a mixture of the bromohydrins, XX and XXI in which the latter was the predominant isomer. The epoxide XXII was not detected, but it seems likely that it was formed and immediately opened to XX, since the pH of the suspension of N-bromosuccinimide was 4.2.

In an alkaline medium where the hydroxyl group is converted to its conjugate base, neighboring group participation should be enhanced (11). In a sodium hypobromite solution, 1,1-dimethylallyl alcohol is converted to the epoxide XXII in 60% yield (11,12). That the dibromide XXIV was not an intermediate in the formation of this epoxide was shown by the fact that the epoxide was formed in the same yield in a sodium hypobromite solution which had been freed of bromide ion (11). Consequently, the reaction seems to proceed as shown by the composite structure XXVIII.

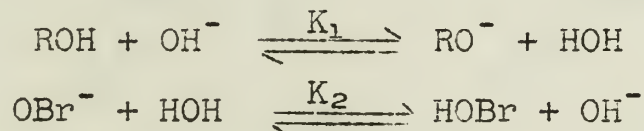


XXVIII

The reaction symbolized by XXVIII may be written as



in which the concentrations of the reactants are governed by the equilibria:



The rate of the reaction may be expressed as

$$-\frac{d(OBr^-)}{dt} = k(RO^-)(BrOH),$$

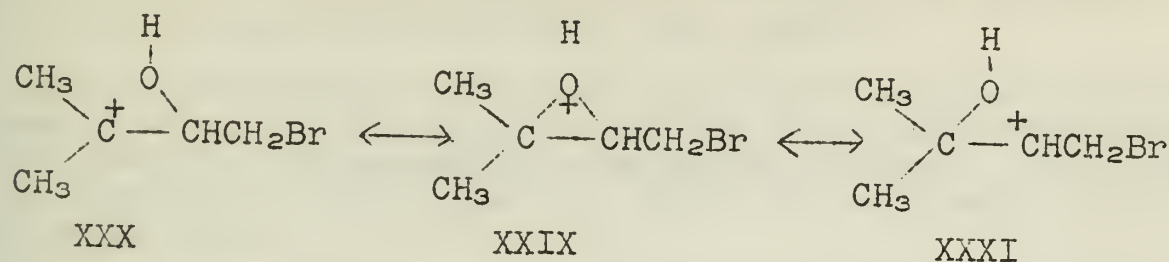
which is easily transformed to

$$-\frac{d(OBr^-)}{dt} = k'(ROH)(OBr^-)$$

The rate constant  $k'$  was found to be independent of the base concentration as predicted by the rate equation (11).

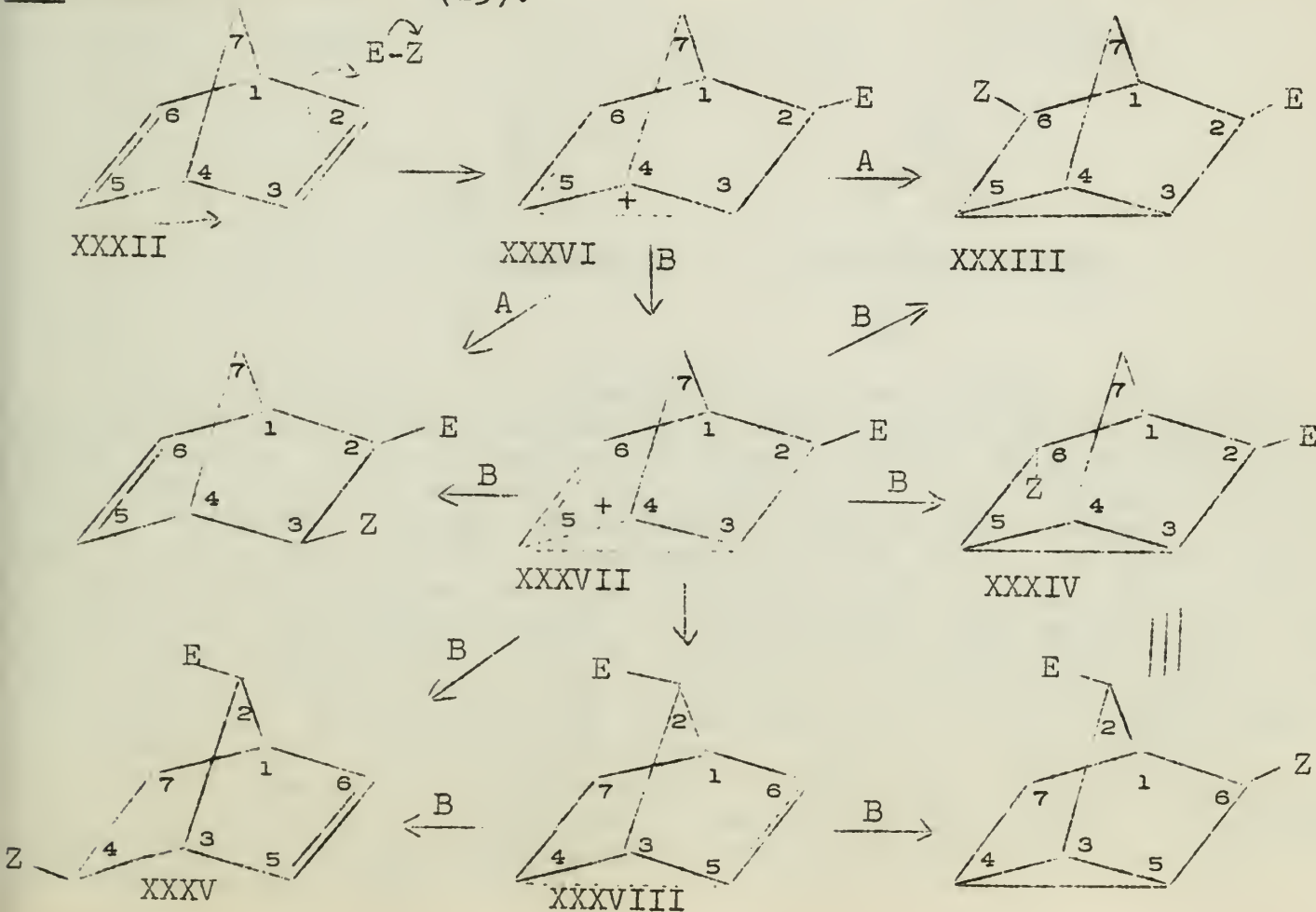


The superiority of the tertiary over the primary hydroxyl as a participating group is in line with predictions based on the driving forces (13) due to participation in substitution reactions and is apparent when the resonance structures of the intermediate oxonium ion XXIX are considered. Alkyl groups on the  $\beta$ -carbon stabilize the positive charge on that carbon and promote cyclization; whereas, on the  $\alpha$ -carbon they promote the normal carbonium ion reaction.



In those addition reactions to 1,1-dimethylallyl alcohol and allyl alcohol which do not involve the neighboring hydroxyl group, the addition is more completely non-Markovnikov in the former case. It seems likely that the geometry of the transition state for the reaction involving the attack of solvent on carbon is such that repulsion between non-bonded atoms is much smaller for the non-Markovnikov than for the Markovnikov addition (11). A similar situation is encountered in the addition to  $\Delta^5$ -cholestene (14).

Control of the addition of bromine to bicycloheptadiene (XXXII) by a neighboring carbon has been observed by Winstein and Shatavsky (15). A mixture of products was obtained, 80% saturated and 20% unsaturated. The saturated products were cis and trans-3,5-dibromonorbornenes (XXXIII and XXXIV). The unsaturated part was at least very largely exo-5-anti-7-dinorbornene (XXXV) which is very reactive in solvolysis (16). The addition of hydrogen chloride or bromide gives largely the exo-5-halonorbornenes (15).





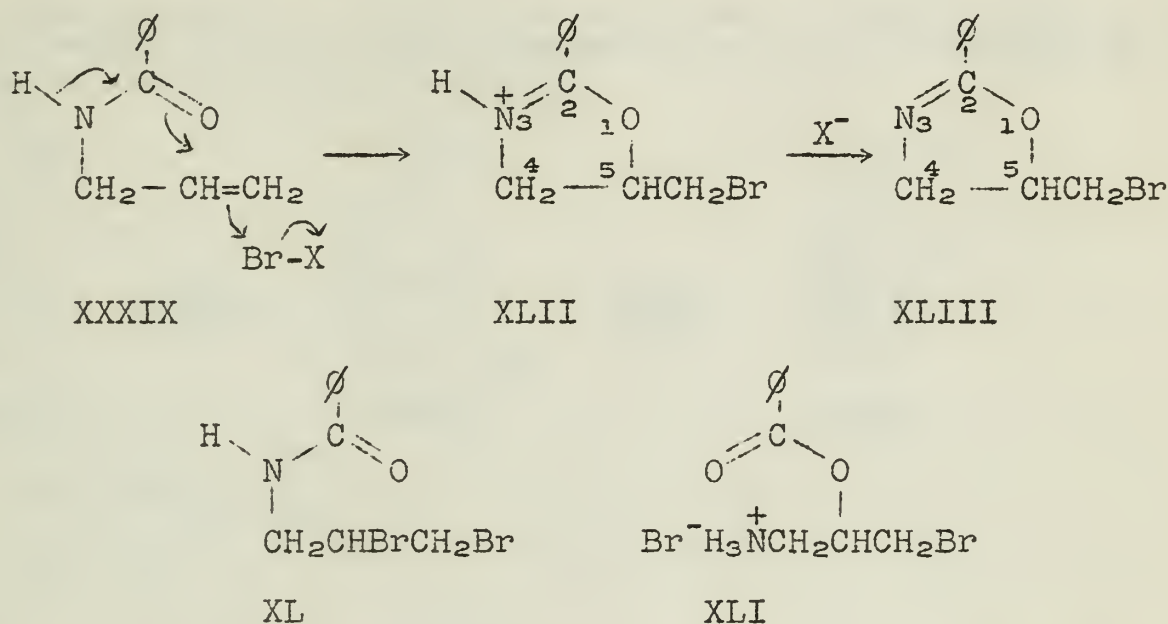




The results of these addition reactions may be understood along the following lines. There is no evidence for any addition process except one involving attack by the electrophilic reagent E-Z on one double bond with anchimeric assistance from the second leading to a homoallylic bridged ion XXXVI, which reacts with a nucleophile either A, before rearrangement, or B, after rearrangement to one or both of the bridged species XXXVII and XXXVIII.

Since 2-benzamido-1-cyclohexyl *p*-toluenesulfonate (18) and 2-benzamido-1-ethyl *p*-toluenesulfonate (19) solvolyze very much more rapidly than the corresponding acetoxy derivatives, the benzamido group may be expected to participate in addition reactions to a greater extent also (17).

Bergmann (20,21) studied the chlorination and bromination of 3-benzamidopropene (XXXIX) in chloroform, and after treating the initial reaction mixture with water obtained the dihalide XL from a normal addition reaction and the hydrohalide of the 3-halo-2-benzoxypopylamine XLI. Although the dihalide XL can be converted to the amine hydrohalide XLI by heating in water or heating to 100°, it is stable under the reaction conditions and therefore cannot be an intermediate in the formation of XLI. This suggests that the reaction proceeds through the oxazolinium halide XLII (17).

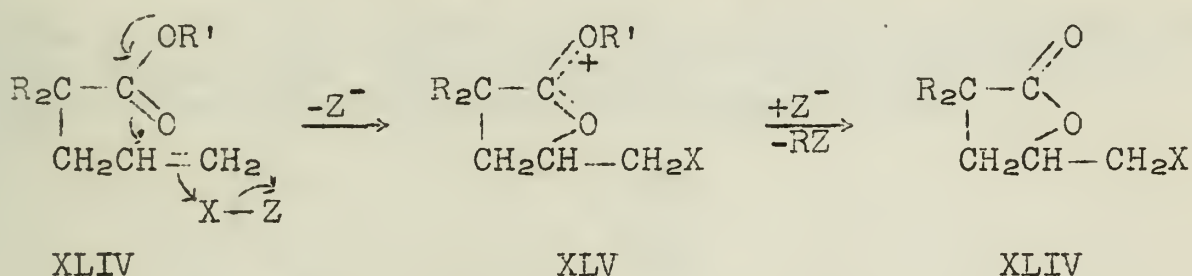


In the bromination of 3-benzamidopropene (XXXIX), 2-phenyl-5-bromomethyloxazolinium bromide (XLII) was obtained as the major product in chloroform, methanol and acetic acid (17,29). In the relatively nucleophilic solvent methanol, the bromoether formed by the addition of the elements of methyl hypobromite to XXXIX was obtained in 20 to 30% yields along with the oxazolinium bromide XLII. In acetic acid, a bromoacetoxy compound was not detected. With a high concentration of bromine and 3-benzamidopropene in both methanol and acetic acid, the prevailing concentration of the oxazolinium bromide XLII tended to be high favoring the intervention of bromide ion and the formation of the dibromide XL. By reducing the concentrations of the reagents employed the formation of the dibromide could be reduced. When N-bromo-succinimide was used in acetic acid, 2-phenyl-5-bromomethyloxazoline (XLI) was obtained in 86% yield free of the dibromide. A *p*-methoxy group enhanced the participation of the benzamido group but the differences were small (2,17).



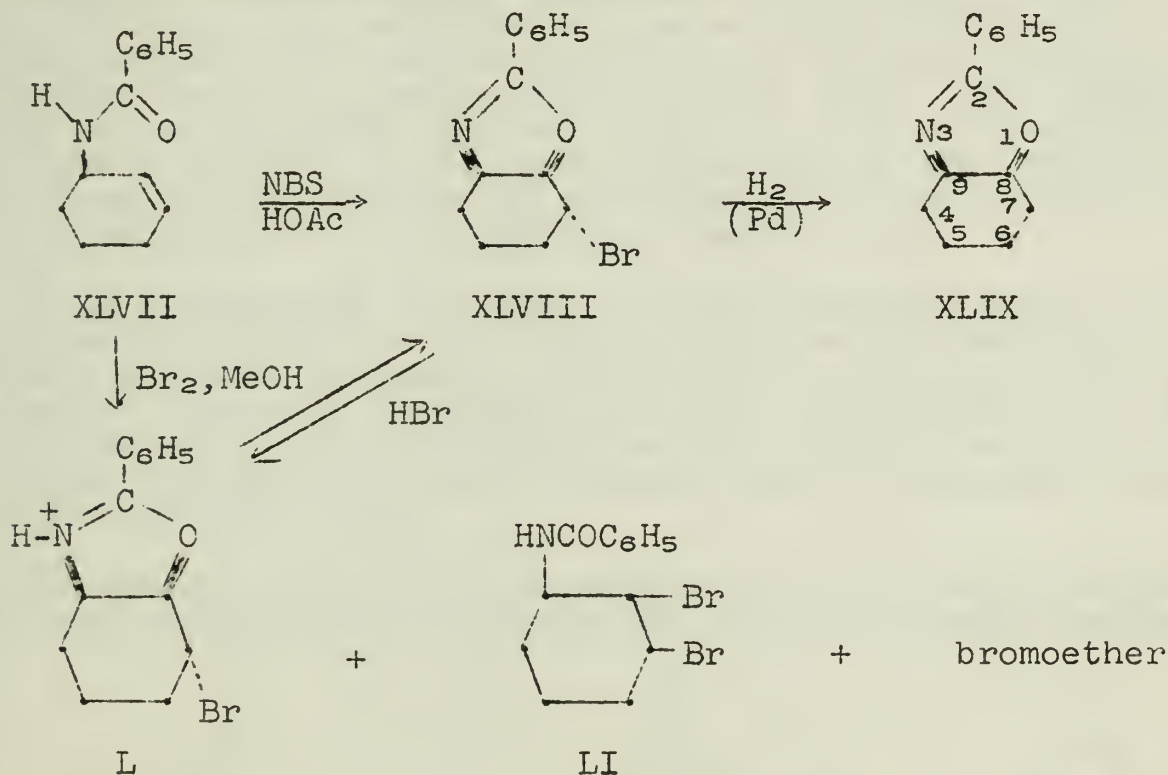
In accord with the decreasing extent of participation in solvolysis of the series of groups  $C_6H_5CONH$ ,  $C_6H_5NHCONH$ ,  $C_2H_5NHCOO$ , and  $CH_3COO$  (19), the addition of bromine to N-allylurethan (21) and N-allylurea (22) gave only dibromides. By contrast, the addition of iodine to the latter compound produced a salt (23) which was presumably the oxazolinium iodide. The addition of chlorine (24), bromine and iodine (25) to N-allylthiourea also gave salts.

The formation of bromo and iodolactones XLVI in the addition of halogens and pseudohalogens to certain unsaturated esters XLIV has been attributed to participation of the carboalkoxyl group (26,27).



An analogous lactonization has been observed in the addition of 2,4-dinitrobenzenesulfonyl chloride to unsaturated acids (28).

The stereochemistry of addition reactions in which there is participation by neighboring has been demonstrated in the bromination of 3-benzamidocyclohexene (XLVII) (29,30).



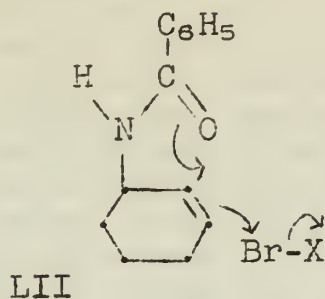
The addition of bromine to 3-benzamidocyclohexene in methanol led to a mixture of 40% oxazolinium bromide L, 32% dibromide LI, and 23% bromoethers. When N-bromosuccinimide was used in acetic acid, 2-phenyl-7-trans-bromo-4,5,6,7-cis-8,9-hexahydrobenzoxazole (XLVIII) was obtained in 85% yield. The presence of the oxazoline ring in the product rather than the six-membered oxazine ring was shown by hydrogenolysis which converted the bromo compound XLVIII to 2-phenyl-4,5,6,7-cis-8,9-hexahydrobenzoxazole (XLIX). The cis-configuration of



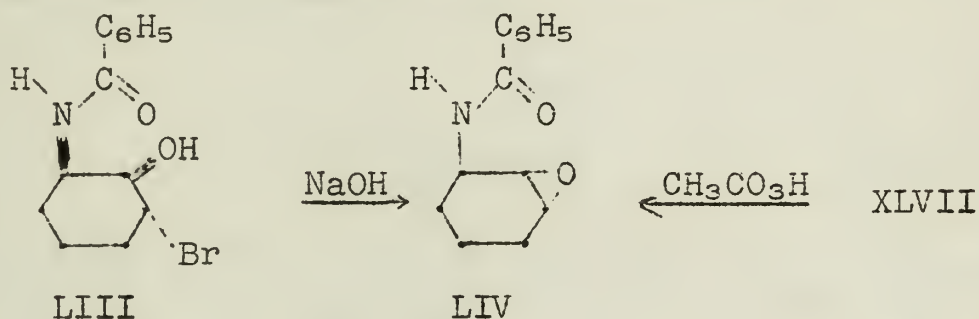




the oxazoline is the one predicted from the mechanism of the addition (30).



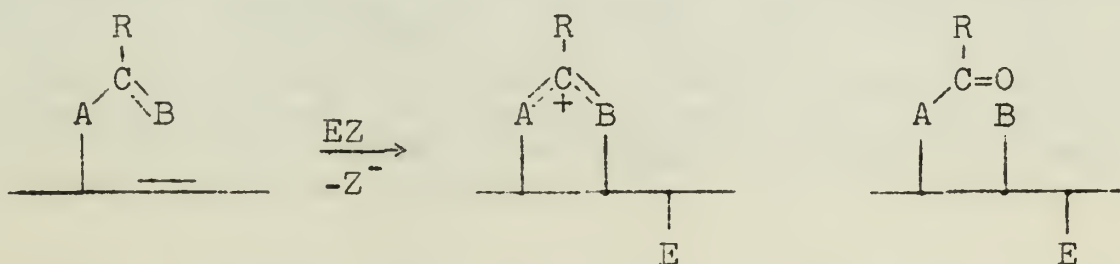
The oxaline salt L was readily converted to the amide XLVII by zinc and acetic acid. When heated with water, the salt L was converted to trans-2-bromo-cis-6-benzamidocyclohexanol (LIII).



A trans relationship of the bromo and hydroxyl groups would also be expected from the mechanism of the addition as shown by LII as well as from the fact that the configuration is retained on hydrolysis of a cis-oxazoline to a cis-benzamido alcohol (18). This trans relationship in the bromohydrin LIII and therefore in the bromo-oxazoline XLVIII was confirmed by the rapid conversion of the bromohydrin in dilute base to the epoxide LIV identical with that formed by the peroxide oxidation of 3-benzamidocyclohexene (30).

It is interesting that the peroxide oxidation which is also an electrophilic addition to an olefinic double bond proceeds without benzamido group participation, and that only the cis-epoxide is formed. This latter result is consistent with the observation (31) that epoxidation of cyclic allylic alcohols occurs on the side of the ring cis to the hydroxyl group and suggests that the benzamido group exerts a similar influence (30).

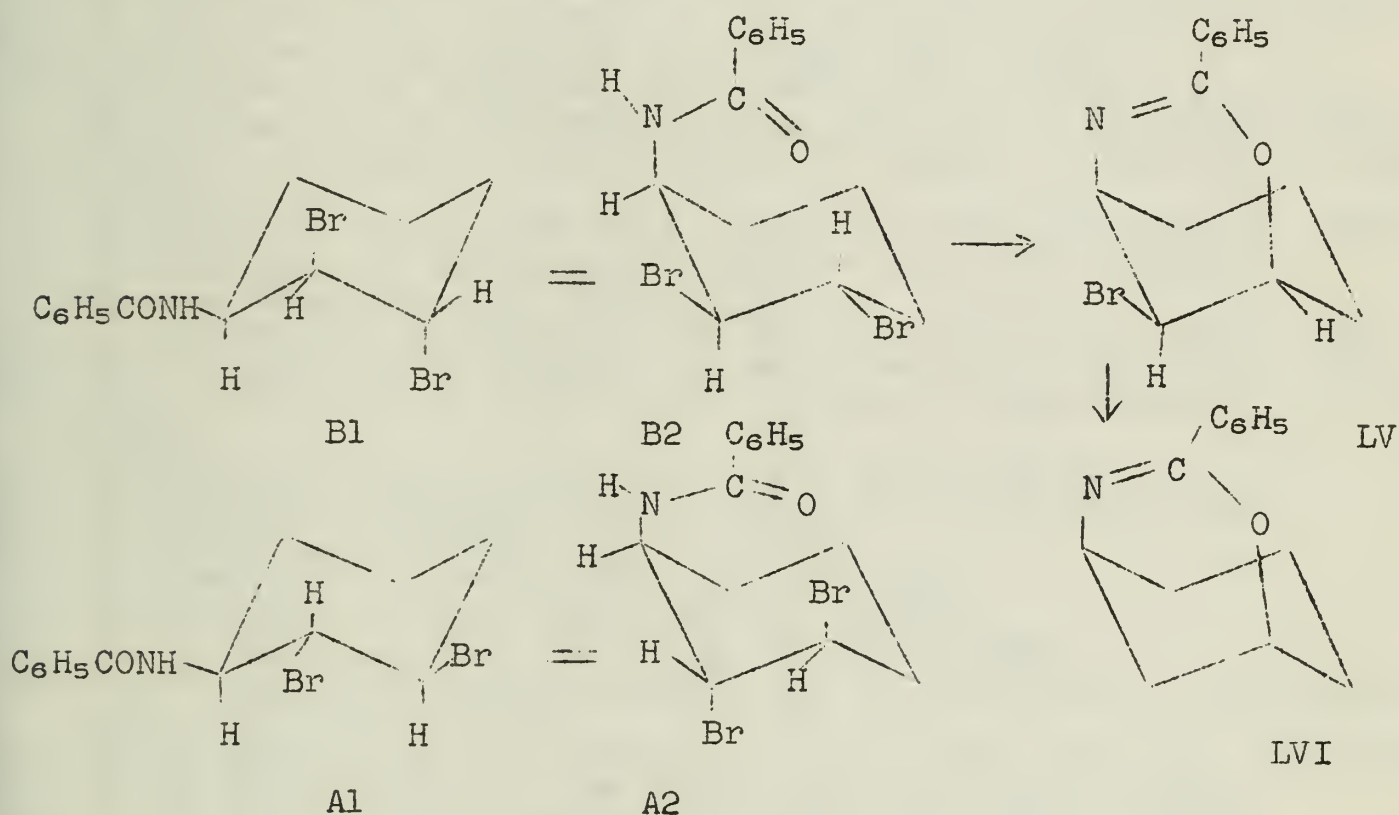
The stereochemistry of the addition reaction with neighboring group participation may be summarized in the following scheme.



It is immediately apparent that such a reaction provides a means of introducing two groups into a molecule in a known stereochemical relationship to a group initially present.



That the benzamido group must compete with bromide ion in the addition of bromine to 3-benzamidocyclohexene (XLVII) is shown by the formation of 87% dibromide LI and only 6% oxazolinium bromide L when the reaction is carried out in acetic acid containing a large excess of lithium bromide. The dibromide consisted of two isomers, A, melting at 183° and B, 125-127°, which were present in a 30:70 ratio. Both dibromides could easily be obtained pure by crystallization and were smoothly converted to 3-benzamidocyclohexene (XLVII) by zinc and ethanol. When either isomer was heated in glacial acetic acid a mixture of the two isomers and a new nitrogen base (LV) isomeric with XLVIII was obtained. In the presence of silver acetate, good yields of the new base were obtained from both dibromides, but the isomer B reacted substantially more rapidly than A. The stability of the new base LV toward hydrolysis and its conversion to the amide by zinc and acetic acid suggested the oxazine structure which was confirmed by hydrogenolysis to the parent oxazine LVI (30).



Tentatively, the isomers A and B have been assumed to be the trans-dibromides arising from a normal trans addition to the double bond. The dibromide A would be able to form an oxazoline only in the highly unfavorable conformation A2; whereas, its isomer B can form an oxazine in the not so unfavorable conformation B2. It is not surprising, then, that the oxazine is formed. Looking at model compounds, trans-3-benzamidocyclohexyl p-toluenesulfonate (32) gives an oxazine in ethanol somewhat more rapidly than trans-2-benzamidocyclohexyl p-toluenesulfonate (18) gives oxazoline.





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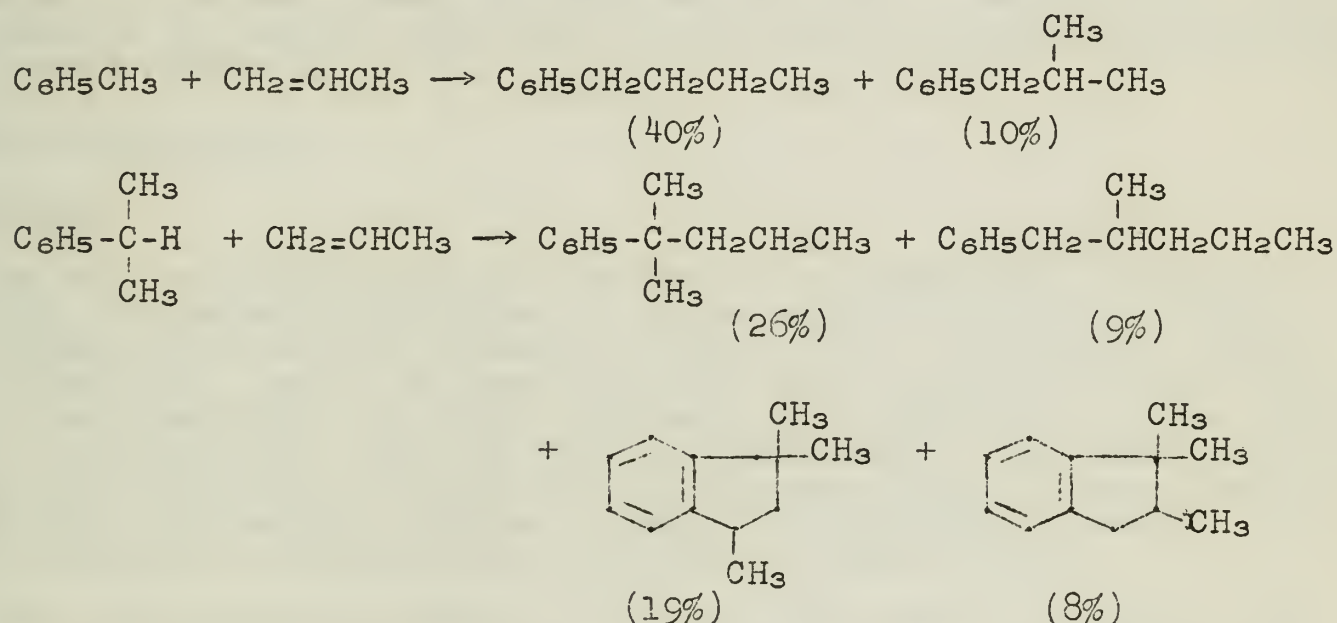
## INTRODUCTION

Although the alkylation of paraffins with olefins in the presence of an acid catalyst such as sulfuric or hydrofluoric acid or aluminum chloride is well known, these catalysts do not cause alkylation of the side chain during ring alkylation of arenes. Side-chain alkylation, however, has been demonstrated recently to occur either by high pressure thermal alkylation or by base-catalyzed alkylation with olefins. The reaction is clean-cut and of high synthetic value.

## GENERAL CONDITIONS

High Pressure Thermal Alkylation

Non-catalytic side-chain alkylation of monoalkylbenzenes with simple olefins has been carried out in a flow-type system (1) under high pressure ( $420 \pm 15$  atm.) at  $400-485^\circ$  and an hourly liquid space velocity of 1.0 or 2.0 (2,3). The alkylated products consist of monoadducts as well as unidentified diadducts. The distribution of the monoadducts is illustrated by propylation of toluene and cumene. The yields, based on the amount of alkylbenzenes which reacted, are given in mole percent (2).



The main reaction products are, however, dimers and trimers of the olefins employed in accordance with the report that olefins undergo polymerization under similar conditions (4). In addition, small amounts of side-chain decomposition products of the arene reactants and adducts are also detected (2,5).

Catalytic Alkylation

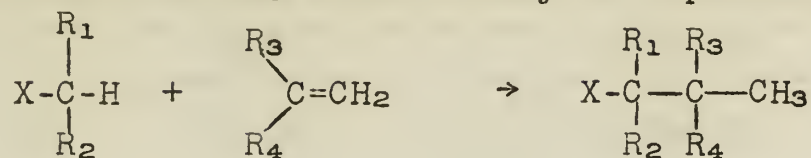
Side-chain alkylation occurs more satisfactorily in the presence of a catalyst. Toluene is known to react with ethylene in the presence of sodium at  $225^\circ$  under a pressure of 900-1000 atm. to form *n*-propylbenzene and 3-phenylpentane (6). The reaction is probably initiated by the formation of benzylsodium, for organolithium compounds have been reported to add to monoolefins (7,8). In fact, it has been shown recently that side-chain alkylation takes place readily in the presence of organoalkali metal compounds (9,10,11,12,13,14).







The main route of the reaction may be represented as



where X may be carbocyclic or heterocyclic with an aromatic character (12), and R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> may be hydrogen or an alkyl group.

The catalyst is a combination of an alkali metal or its hydride with an organic compound of the general formula RY, where R may be alkyl, alkenyl, cycloalkyl, aralkyl or aryl, and Y may be hydrogen, halogen, hydroxyl, carbonyl, alkoxyl, nitro or cyanogen. The organic compound serves as promoter and presumably reacts with the alkali metal under the experimental conditions (11,12). The organoalkali compound itself may be used as a catalyst to insure homogeneity of the reaction mixture (15,16).

Side-chain ethylation is relatively easy and usually occurs at 200-225° at 30 atm. initial pressure. Diethylation usually accompanies monoethylation when more than one α-hydrogen atom is available (11). More severe conditions are required, however, with higher olefins. Thus, propylation of toluene takes place at 300° and 90 atm., and isobutylation of toluene occurs at 350° and 200 atm. pressure (10). The main products of typical side-chain alkylation of aromatic hydrocarbons are listed in Table I.

## GENERAL OBSERVATIONS

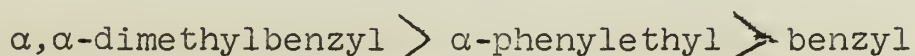
### Orientation

The mode of addition of alkylarenes to unsymmetrical olefins in catalytic, side-chain alkylation is illustrated by propylene, which with toluene gives mainly isobutylbenzene (5,10). In thermal, side-chain alkylation, where the reaction apparently proceeds by free radicals, the orientation is found, however, to be dependent on the structures of the reactants and the reaction temperature. The selectivity ratios, defined as the ratio of the alkylarene product formed from the more stable intermediate radical to the alternate-addition adduct, of typical competing reactions are described in Table II (2).

From the selectivity data, it can be seen that the order of the relative ease of formation of the intermediate monoadduct radicals decreases in the series



Comparable selectivity has been reported in the addition of methyl radicals to propylene and isobutylene (17). Furthermore, the selectivity among the aralkyl radicals toward a given olefin decreases in the order

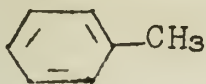
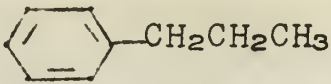
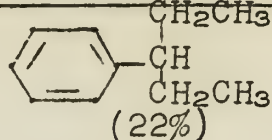
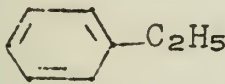
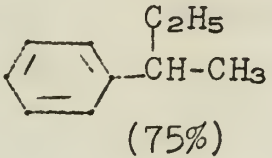
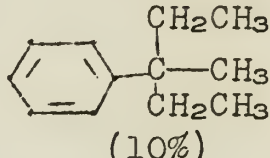
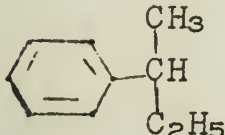
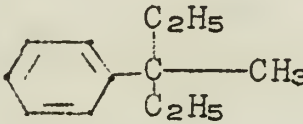


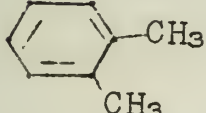
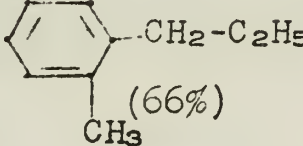
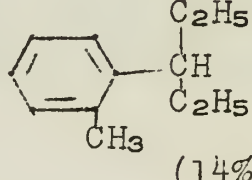

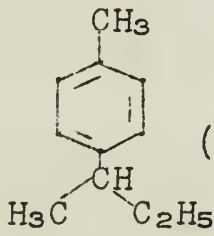
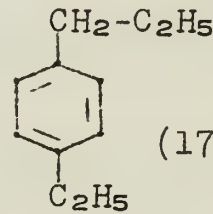
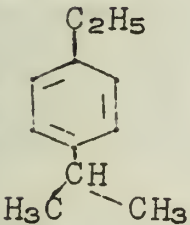
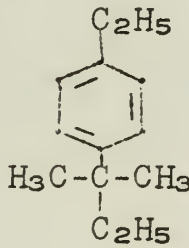
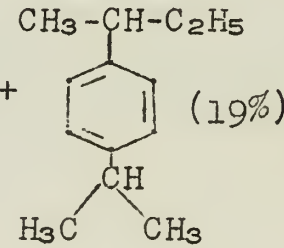

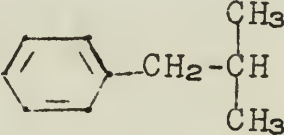

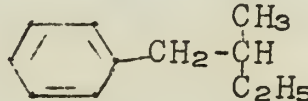

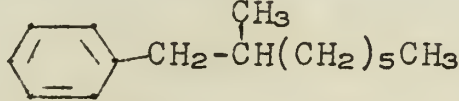


or, in general, the most stable benzylic radicals are the most selective in addition to unsymmetrical olefins. It should be noted that this selectivity tends to decrease with elevation in temperature, probably because of enhanced activation of the reacting species (2).



Table I

## Catalytic Side-chain Alkylation of Aromatic Hydrocarbons

No.	Arene	Olefin	Products	Ref.
1.		$\text{CH}_2=\text{CH}_2$	 +  (57%) (22%)	11
2.		$\text{CH}_2=\text{CH}_2$	 +  (75%) (10%)	11
3.		$\text{CH}_2=\text{CH}_2$	 (90%)	11
4.		$\text{CH}_2=\text{CH}_2$	 (50%)	11
5.		$\text{CH}_2=\text{CH}_2$	 +  (66%) (14%)	11
6.		$\text{CH}_2=\text{CH}_2$	 (48%) +  (17%)	23
7.		$\text{CH}_2=\text{CH}_2$	 (20%) +  (19%)	23
8.		$\text{CH}_3\text{CH}=\text{CH}_2$	 (10%)*	10
9.		$\text{CH}_3\text{CH}_2\text{CH}=\text{CH}_2$	 (9%)*	10
10.		$\text{CH}_3(\text{CH}_2)_5\text{CH}=\text{CH}_2$	 (7%)*	10

\*These yields are based on the olefin charge. The rest are based on the amount of arenes which reacted.







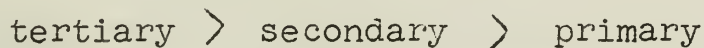
TABLE II

## Selectivity Ratios in Thermal Alkylation

Competing intermediate radical types	Reactants	Temperature		
		405°	430°	455°
Secondary vs. primary	$\text{C}_6\text{H}_5\text{CH}_3 + \text{CH}_2=\text{CHCH}_3$	4.4	5.1	4.1
	$\text{C}_6\text{H}_5\text{C}_2\text{H}_5 + \text{CH}_2=\text{CHCH}_3$	6.5	6.6	4.2
	$\text{C}_6\text{H}_5-\underset{\text{CH}_3}{\overset{\text{CH}_3}{\text{CH}}} + \text{CH}_2=\text{CHCH}_3$	13	7	9
Tertiary vs. primary	$\text{C}_6\text{H}_5\text{CH}_3 + \text{CH}_2=\underset{\text{CH}_3}{\text{C}}-\text{CH}_3$	45	35	20
	$\text{C}_6\text{H}_5\text{C}_2\text{H}_5 + \text{CH}_2=\underset{\text{CH}_3}{\overset{\text{CH}_3}{\text{C}}}-\text{CH}_3$	all tertiary		
Tertiary vs. secondary	$\text{C}_6\text{H}_5\text{CH}_3 + \text{CH}_3-\underset{\text{CH}_3}{\text{C}}=\text{CHCH}_3$	all tertiary		

Structural Effects

The reactivity of olefins decreases with alkyl substitution on the unsaturated carbon atoms of the olefins in side-chain alkylation (2,11). This phenomenon is also observed in thermal alkylation of paraffins with olefins (18) and may arise from the steric or electronic inductive effect of the alkyl substituents. On the other hand, the ease of replacement of the  $\alpha$ -hydrogen atoms of arenes by an alkyl group in the presence of sodium decreases in the order



as is shown by ethylation of p-ethyltoluene and p-ethylcumene in Table I. Thus the steric factor is not the sole criterion in catalytic, side-chain alkylation.

Catalytic, side-chain alkylation may be related to the relatively familiar base-catalyzed additions of very weak acids to activated olefinic systems as typified by the addition of alcohols, amines and acidic hydrocarbons to acrylonitrile (19), butadiene (20), and styrene (21). Amines have been reported to be alkylated by the present method, but at relatively higher temperature (16). So a correlation between the acidity of the aromatic compound and the reaction temperature seems to exist: the smaller the  $\text{pK}_a$  (22) of the aromatic compound the higher the temperature of the  $a$  reaction.

Relative Rates

The relative rates of side-chain ethylation of various alkylbenzenes in the presence of sodium and anthracene has been determined by means of competitive reactions (23). The relative rates are

Toluene 1.0, ethylbenzene 2.8, n-propylbenzene 1.2, isopropylbenzene 1.9, sec-butylbenzene 0.57, indan 1.35, o-xylene 1.9, m-xylene 1.6, p-xylene 0.62, p-cymene 0.75 and p-t-butyltoluene 0.21.

The results show that methyl substitution of a benzylic hydrogen increases the rate of ethylation even though these compounds do not undergo metalation as readily as toluene (24,25). Since metalation is most likely to be the initial step in catalytic, side-chain alkyl-

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1. The first group of people who are interested in the study of the history of the world are the historians. They are people who study the past and try to understand what happened and why it happened. They use a variety of sources, including books, documents, and artifacts, to reconstruct the past. They also try to understand the people who lived in the past and how they thought and felt. Historians are interested in the past for a variety of reasons. Some are interested in the past because they want to know what happened and why it happened. Others are interested in the past because they want to understand the people who lived in the past and how they thought and felt. Still others are interested in the past because they want to learn from the mistakes of the past and avoid them in the future.



ation (26), it implies that the acidity of arenes too is not the dominating factor in this type of reaction. The relatively small rates of ethylation of *p*-dialkylbenzenes indicates that the inductive effect of alkyl substituents also influences the rate of alkylation.

In thermal alkylation, the relative rates of toluene, ethylbenzene and cumene are 1.0, 0.8 and 0.125, respectively (2). This order of decreasing reactivity is in accord with the bond dissociation energies (27) and the ease of abstraction of the benzylic hydrogens with free radicals (28,29).

### Nature of Catalysts

Lithium is found to be a less effective catalyst than sodium, and their hydrides are found to be still less reactive in side-chain alkylation. When potassium is used as a catalyst, cyclization to indans also occurs besides normal alkylation. This may be due to the relatively more active carbanion produced by potassium (24,30).

The yields of the alkylated products also vary with the promoter used. The relative effectiveness of various promoters are determined by ethylating toluene at 200-225° for 4 hours in the presence of sodium and a promoter (11). The observed order in decreasing effectiveness of various promoters is

anthracene > *o*-toluic acid > *o*-chlorotoluene > *o*-bromotoluene, benzonitrile > allyl chloride > di-*t*-butylperoxide > pyridine > fluorene > *sec*-butylchloride > *m*-cresol > dihydroanthracene > benzyl chloride.

### Side Reactions

Isomerization of the olefin reactants might be expected during side-chain alkylation in the presence of organoalkali compounds, since these catalysts are known also to catalyze isomerization of olefins (31,32,33,34). Thus in the reaction of toluene with 1-octene, the recovered olefin consists predominantly of *trans*-octenes (10), which, presumably less reactive than 1-octene, evidently have not taken part in alkylation.

Also small amounts of hydrogen, olefin polymers and the saturated hydrocarbons of the corresponding olefins have been detected (10). Only slight evidence is seen that side-chain cleavage by sodium catalyst has taken place.

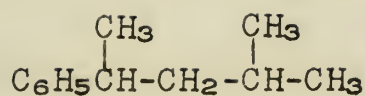
An interesting side-reaction is cyclization to indans (2,35). The distribution of normal alkylation products and indans in this type of reaction is illustrated in Table III (35).

The reaction of isopropylbenzene with propylene indicates that the cyclization reaction does not show the selectivity that the simple alkylation reaction does. Table III further shows that the rate of indan formation as compared to the normal product increases with increasing substitution on the  $\alpha$ -carbon atom of the arene reactant.

Another striking feature is monoadduct rearrangement. The following examples of 1,2-phenyl migrations have been noted during thermal, side-chain alkylation (2).







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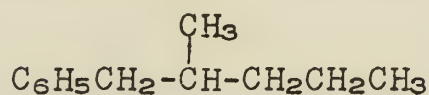
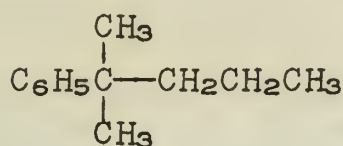
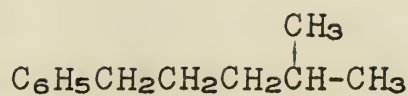
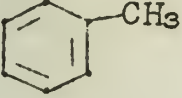
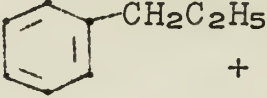

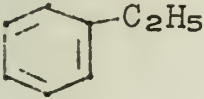


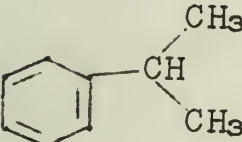
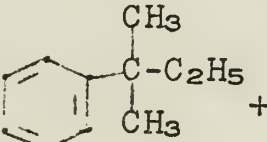
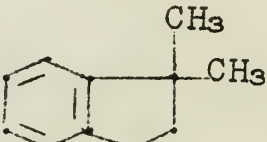
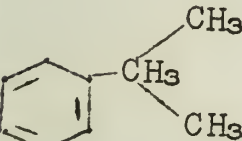
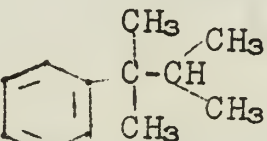
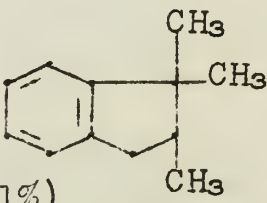
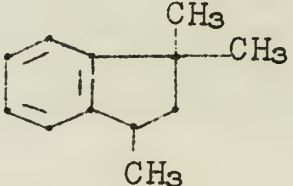
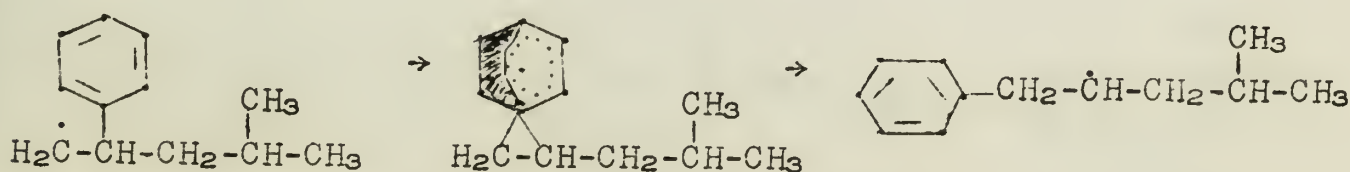


TABLE III  
Potassium-catalyzed Alkylation

Aromatic Hydrocarbon	Olefin	Products	
	$\text{CH}_2=\text{CH}_2$	 +  (52%) (1%)	
	$\text{CH}_2=\text{CH}_2$	 +  (55%) (9%)	
	$\text{CH}_2=\text{CH}_2$	 +  (29%) (10%)	
	$\text{CH}_3\text{CH}=\text{CH}_2$	 +  (2%) (1%) +  (1%)	

A mechanism, similar to that suggested previously to account for phenyl migration in the neophyl radical (36) and decarbonylation of aldehydes (37) would be the following:



The initial primary radical might be formed by direct hydrogen abstraction or homolytic thermal cleavage.

1. The first part of the report is a general introduction to the subject of the study. It discusses the importance of the problem and the objectives of the research.

### 2. Methodology

The methodology section describes the research methods used in the study. It includes a detailed description of the data collection process and the statistical analysis techniques employed.

The results of the study are presented in this section. It includes a summary of the findings and a discussion of their implications for the field of study.

Conclusion

(1)

Conclusion

Conclusion

Conclusion

The study has shown that the proposed method is effective in solving the problem. The results are consistent with the theoretical predictions and provide a basis for further research.

References

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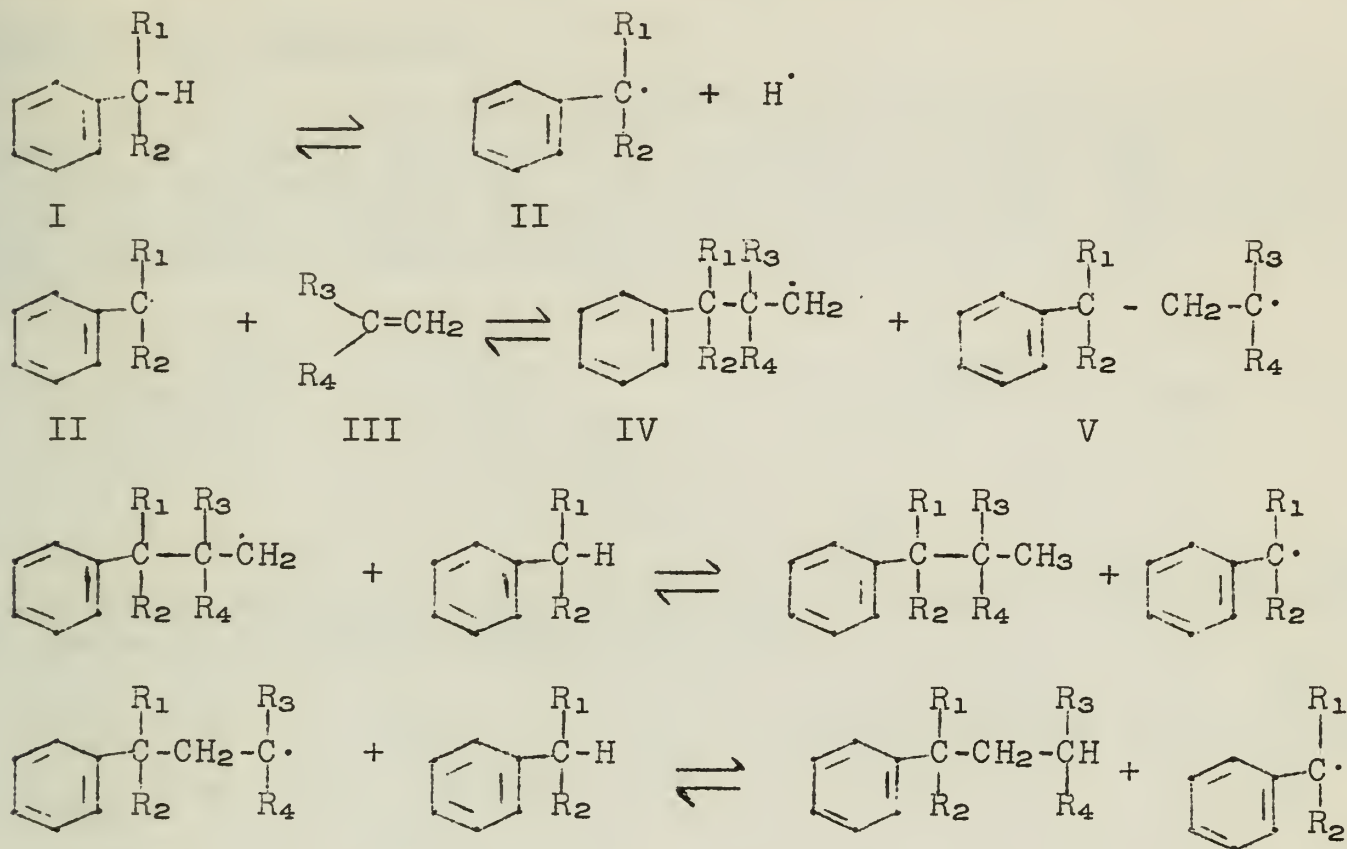
References

The study was supported by the National Science Foundation. The author wishes to thank the reviewers for their helpful comments.

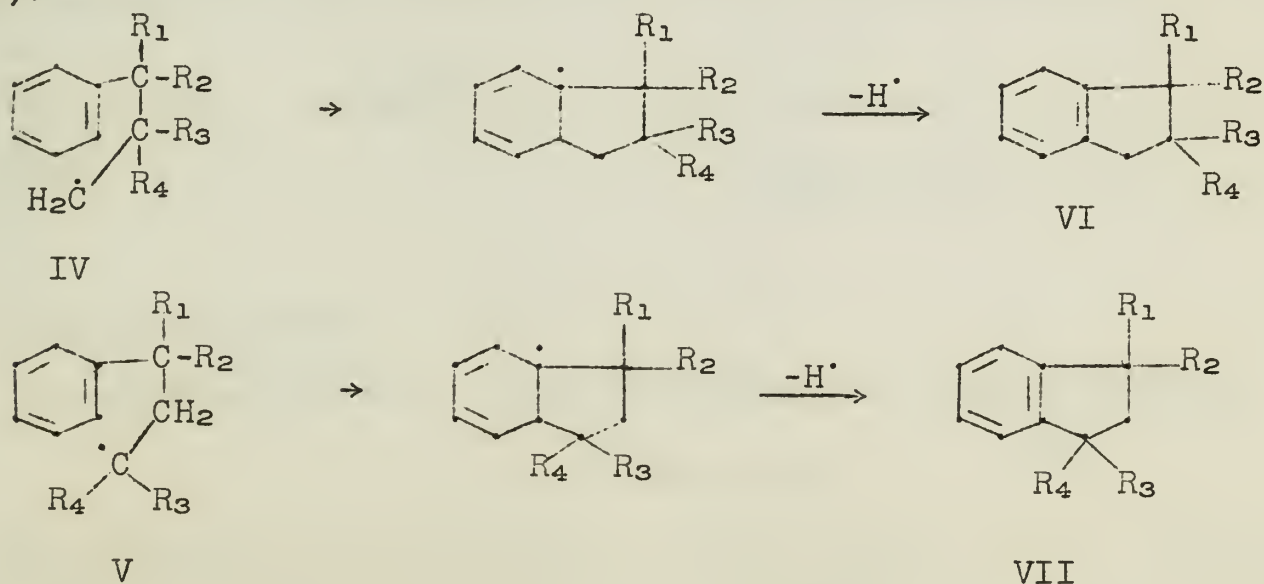
## MECHANISMS

Radical Chain Mechanism

High pressure thermal alkylation apparently proceeds by free radical mechanism with the benzylic radical II, most probably produced by direct pyrolytic homolysis of the arene reactant I, serving as chain-propagator (2).



Both radicals IV and V should be expected from the addition of the benzylic radical II to olefin III, since high temperature addition of alkyl radicals to olefins has been found to yield products of both modes of addition (17,18,38). The radicals IV and V can also undergo cyclization to indans VI and VII, respectively, as similar cyclization of 4-phenyl-1-butyl free radical to tetralin has been reported recently (36,39).





The first part of the paper is devoted to the study of the properties of the function  $f(x)$  defined by the equation

$$f(x) = \int_0^x \frac{1}{1+t^2} dt$$

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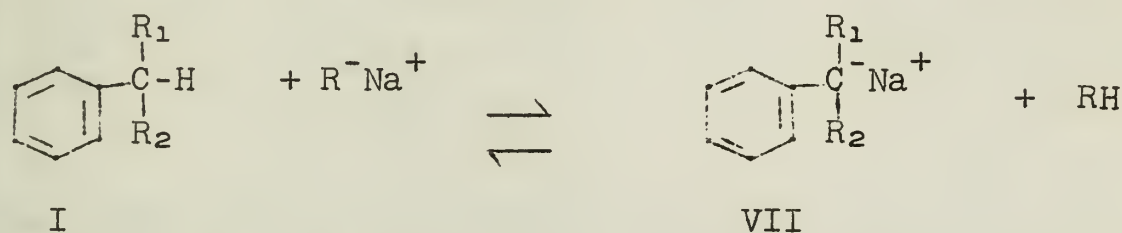
$$f(x) = \arctan x$$

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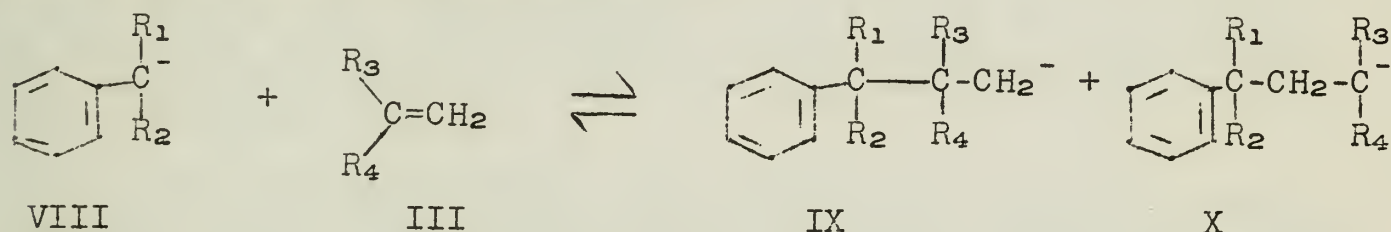
The formation of VI may have more chance than that of VII, for the geminal effect of substituents is known to be maximum in accelerating the reaction when they are situated on the carbon atom in the middle of the chain which closes to form a 5-membered ring (40). The possibilities such as the disproportionation of the intermediate radicals IV and V into hydrogen or alkyl radicals (5), and coupling between radicals leading to chain termination should not be excluded.

### Carbanion Chain Mechanism

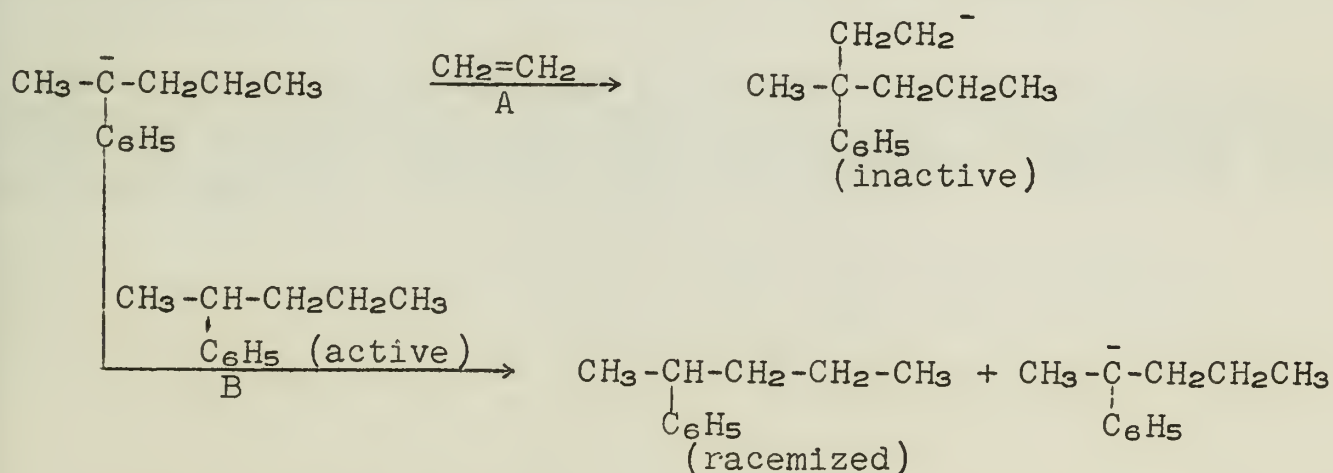
In catalytic, side-chain alkylation, the function of promoter is evidently to initiate the reaction by forming an organoalkali compound, RNa, which then metalates the arene reactant I (10,11), the  $\alpha$ -position in the side chain being a favored point of attack (24). The organo-sodium compounds are best considered as polar, undissociated ion pairs (24,30).



The carbanion of VII can then add to the olefin III to form most preferably the stable primary carbanion IX (10).



That the abstraction of a proton from the arene I by the carbanion VIII is not likely is demonstrated by ethylation of the optically active 2-phenylpentane. Here the recovered aromatic hydrocarbon is only slightly racemized, although extensive racemization occurs when ethylene is omitted. These facts show that in the following equations, the reaction proceeds much faster via path A than via path B (26).



The carbanions IX and X can now suffer several fates. Since IX is presumably predominant of the two, only its reactions will be considered here. First, it can abstract a benzylic hydrogen from arene I to form

The first part of the report deals with the general situation of the country and the progress of the work. It is followed by a detailed account of the various expeditions and the results obtained. The report concludes with a summary of the findings and a list of references.

REPORT ON THE PROGRESS OF THE WORK

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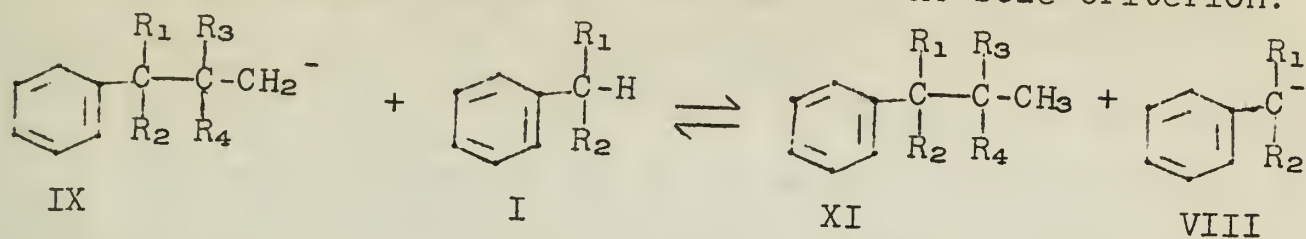
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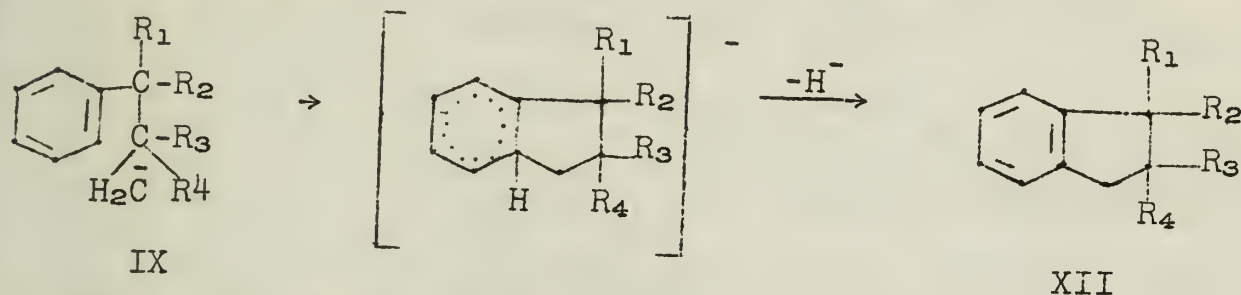
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the monoalkylated product XI and liberate a new molecule of carbanion VIII for chain propagation (10,11). The nucleophilicity of the carbanions VIII and IX is most likely the dominating factor in this chain reaction, since as has been mentioned earlier neither the steric effect nor the acidity of the arene reactant is the sole criterion.

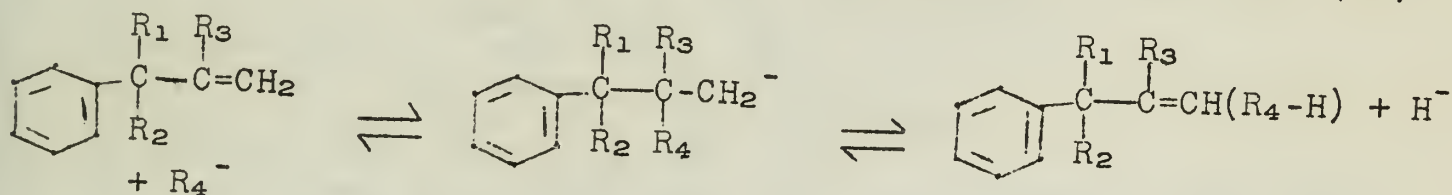


Secondly, the carbanion IX can attack the aromatic nucleus to form the indan XII (35).



This latter route might be expected to be less favorable, since the nuclear hydrogen is less acidic than a benzylic proton (30). However, the increasing bulk of R<sub>1</sub> and R<sub>2</sub> might favor this reaction; because the chain propagation step is then reduced as the benzylic hydrogen atom becomes less active (24), and the steric effect of R<sub>1</sub> and R<sub>2</sub> tends to hold the carbanion IX in close proximity to the aromatic ring facilitating the cyclization reaction. This reasoning has been supported by experimental evidence (10).

Thirdly, the carbanion IX may also undergo the following competitive reactions (10), since alkali alkyls have been reported to decompose into alkali hydrides and olefins at temperatures above 100° (41).



The hydride can either add to olefin III to form ultimately the corresponding paraffin or abstract a proton from the arene reactant I to form the benzylic carbanion VIII and hydrogen. These side products have been detected during experiments (31,32).

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## APPLICATIONS OF MICROWAVE SPECTROSCOPY TO ORGANIC CHEMISTRY

Reported by W. S. Smith

October 27, 1958

Microwave spectroscopy had its inception in 1934 (1), but no further work appeared in the literature until 1946. This delay was due primarily to a lack of equipment. Research on microwave radar during World War II provided the instruments and stimulus for further development in the period following. The past few years have seen the expansion of the microwave region until it now overlaps the far infrared region. This seminar will consider microwave spectroscopy from a qualitative view and point out its applicability to organic chemistry, its limitations, and some of the results obtained to date.

The microwave region comprises that part of the electromagnetic spectrum which lies between the far infrared and the radiofrequency region. There are no definite boundaries to this region, but it is usually regarded as extending from about 1mm. to 30cm. in wavelength (300,000mc. to 1000mc.) (2). Its position in the overall spectrum is shown in Fig. 1:

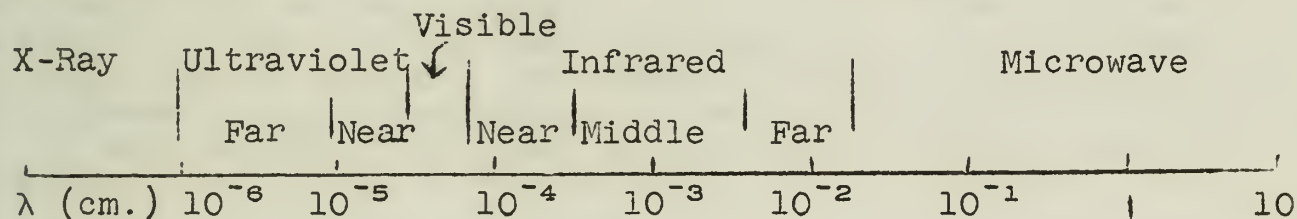


Fig. 1

Spectroscopy in each of these regions has its own characteristic techniques and its own advantages and disadvantages. In the visible and ultraviolet regions, transitions between electronic energy states are observed; in the infrared region vibrational spectra are observed; and in the microwave region pure rotational spectra are observed. In addition, the microwave region is distinguished from the infrared and ultraviolet regions because of the basically different methods of generating, detecting and measuring the radiation. The microwave region is the only spectral region in which an essentially monochromatic source of radiation is available. In the infrared, for example, the source produces all of the frequencies which are to be used; this makes it necessary to use an optical system for separation of these frequencies and results in a loss of resolution. No such difficulty is found in the microwave region, and extremely high resolution with consequent accuracy of measurement is probably the most distinguishing feature of this region.

## MICROWAVE SPECTROGRAPHS

A simplified block diagram of a typical microwave spectrograph is shown in Fig. 2.

Department of the Interior

Department of the Interior

The Department of the Interior is pleased to announce that it has received a grant from the National Science Foundation to support a research project on the geology of the Colorado Plateau. The project will be conducted by the U.S. Geological Survey, Denver, Colorado, and the University of Colorado, Boulder, Colorado. The project will focus on the geology of the Colorado Plateau, which is a large area of land in the southwestern United States. The project will involve a series of field studies and laboratory analyses to determine the geology of the Colorado Plateau. The project will also involve the development of a map of the Colorado Plateau. The project is expected to be completed in 1980.

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Denver, Colorado  
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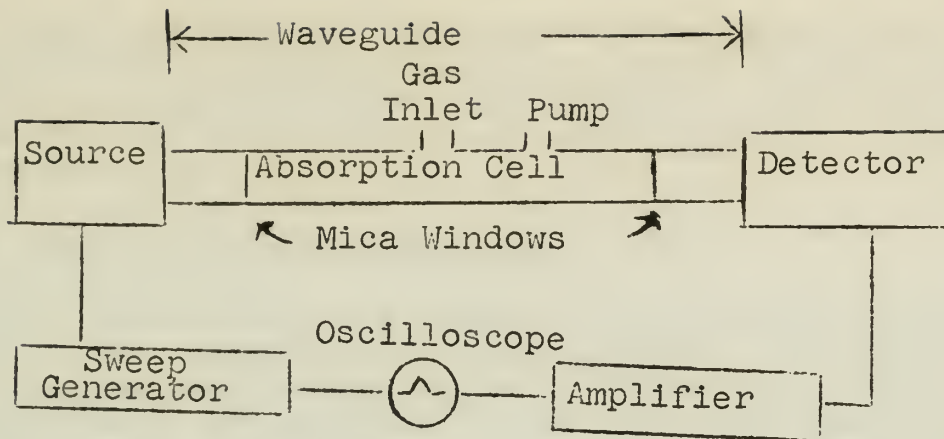


Fig. 2

Microwave absorption is detected by passing radiation from the source through a waveguide absorption cell containing the sample and measuring the amount of absorption as a function of the source frequency. The most commonly used source of energy is the reflux klystron, which is available commercially for frequencies up to about 60,000mc. Ordinary vacuum tube oscillators are unsatisfactory for operation at microwave frequencies because of the transit time required for the electron to pass between the electrodes; the klystron takes advantage of this transit time and functions satisfactorily as an oscillator at extremely high frequencies. To scan the desired frequency range, it is only necessary to tune the klystron either manually or automatically.

After passing through the sample, radiation is detected by a crystal detector and amplified. The absorption pulse is displayed as a vertical deflection on an oscilloscope whose horizontal base is calibrated in terms of frequency. The exact frequency of the absorption is measured by superimposing on the horizontal sweep a set of frequency markers which are controlled by a frequency standard. The frequency standard is in turn controlled by comparison with transmissions from WWV, the National Bureau of Standards Station in Washington. In this way, the frequency of absorption can be measured with an accuracy of  $\pm 50$ -100kc. In addition to the oscilloscope presentation of data, a strip-chart recorder may be used to provide a permanent record.

The sensitivity of the microwave spectrograph can be improved by placing an electrode in the waveguide absorption cell and using a low frequency electric field to modulate the absorption line. This procedure is called Stark modulation and is used in almost all spectrographs. The two principal advantages of this method are that it minimizes the effect of power variations in the waveguide and in the source, and it permits the use of a tuned radiofrequency receiver to reduce the low frequency noise generated by the crystal detector, thus increasing sensitivity.

## APPLICATIONS

### General Requirements

There are two major limitations on the type of substance which can be studied in the microwave region. The molecule must have a permanent dipole moment, electric or magnetic, and must have a vapor

1900



pressure of approximately  $10^{-3}$  mm.-Hg at the temperature of observation. Since microwave spectrographs can now be operated at temperatures up to  $1000^{\circ}\text{K}$ , the vapor pressure requirement is not a serious limitation except for the large number of molecules which dissociate at high temperatures (3).

### Qualitative Identification of Compounds

Microwave spectroscopy is capable of providing certain and rapid identification for hundreds, if not thousands, of chemical compounds. The high resolution obtainable in this region means that lines of two different substances are generally well separated and easily differentiated. For example, the spectra of different isotopic species of the same molecule are almost always easily resolved and identified. The positions of pure rotational lines depend only on the principal moments of inertia of the molecule as a whole; these lines cannot, therefore, be used to identify component groups within a given molecule as can vibrational lines in the infrared region. However, the extreme sensitivity of the rotational spectrum to very slight changes in structure, plus the resolution obtainable, makes the microwave spectrum of a compound so specific that measurement of only one or two lines serves to identify that compound uniquely. High resolution also makes it possible to isolate and identify lines of a large number of substances in one gaseous mixture (4).

Another natural advantage of microwave spectroscopy is the small amount of gas required to detect absorption. The typical absorption cell has a volume of only several cubic centimeters and is filled to a pressure of around  $10^{-2}$  mm.-Hg. This corresponds to only a few micrograms of material. The sample is not damaged during the analysis and may be recovered in most cases.

The microwave region between 1mm. and 3mm. shows great promise for the study and identification of molecules. Since spectral lines usually increase in intensity roughly as the square or cube of the frequency, it is often much easier to find lines of a given molecule which meet the intensity requirements in the millimeter than the centimeter region. The region from 1-3mm. covers a span of 200,000mc. Assuming that lines 100kc. apart can be separated and identified, Gordy has pointed out that there are 2,000,000 spectral spaces available in this range alone--more than in all the rest of the microwave region (5). It is interesting to compare this figure with the number of spectral spaces available in the infrared. On the assumption that an average resolution of  $1\text{cm.}^{-1}$  is attainable over the entire region, there are only 10,000 spectral spaces available in the infrared.

Microwave spectra can be tabulated as a list of frequencies instead of a series of curves since individual lines are normally resolved and measured. Kisliuk and Townes (6) have prepared a list of 1800 known microwave lines of 92 different substances. Thus, identification of a compound, or mixture of compounds, can be made by measuring a series of lines and comparing them with a table of known lines. There is very little possibility of confusion due to overlap of lines because of the high resolution of the method. Of the 1800 lines<sup>in</sup> the table mentioned above, only ten cases were found where two lines of different substances were closer than 0.25mc.





At the present time it is not very practical to scan over the entire microwave region since several different oscillators would have to be used, but this difficulty can probably be obviated by the adoption of a standard region in which everyone can work. Another difficulty at present is that most of the lines which have been tabulated are for the simple molecules which have relatively few lines. The list of tabulated lines has resulted chiefly from structural studies, and these studies have dealt primarily with those simple molecules whose spectra and structures could be correlated with relative ease. Townes believes that it is doubtful whether microwave spectroscopy will be very successful with molecules having more than about 25 atoms. As the size of the molecule increases, rotational lines may be split into multiplets with each component so weak that detection is difficult (7).

### Measurement of Bond Lengths and Bond Angles

The rotational energy for a diatomic molecule is given by the expression:

$$E = \frac{h^2}{8\pi^2} \frac{J(J+1)}{I} = hBJ(J+1)$$

where  $h$  is the Planck constant,  $I$  is the moment of inertia of the molecule and  $J$  is the rotational quantum number. The quantity  $B$  is called the rotational constant and is equal to  $h/8\pi^2I$ . The frequency observed when the molecule makes a transition from a lower to a higher rotational energy level is therefore:  $\nu = 2B(J+1)$ , where  $J$  is the quantum number for the lower state. The moment of inertia of a diatomic molecule is  $I = \mu r^2$ , where  $\mu$  is the reduced mass and  $r$  the interatomic distance. If the atomic masses are known, measurement of the rotational absorption lines gives directly the interatomic distance.

In the case of polyatomic molecules the moment of inertia is related to bond lengths and angles in a more complex manner; many times there are more independent structural parameters to be determined than there are measurable moments of inertia. When this is the case, the structure cannot be completely determined from the rotational spectrum without employing isotopic substitution. Since the bond distances are determined primarily by the electrical properties rather than the masses of the atoms, it is possible to obtain additional equations involving the interatomic distances and the spectral constants by substituting isotopes in the molecule. Many atoms have naturally occurring isotopic species present in reasonable concentrations, and their spectral lines may often be observed along with lines of the common species. In general, however, only one substitution at a given location in the molecule will yield additional independent equations (9). A large number of organic molecules have been studied in this way, and complete structures have been established for many from microwave data alone (10). In cases where it is not possible to obtain sufficient isotopic combinations for an unambiguous structure determination from microwave data alone, a combination of microwave data and data from other sources can be used (11).

A complete microwave analysis of the pyridine molecule has recently been made (12,13). The microwave spectra of six isotopic species were examined in the 18-27kmc. region. The six isotopes used were pyridine, 2-deutero, 3-deutero, 4-deutero, 2-C<sup>13</sup> and 3-C<sup>13</sup>.



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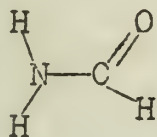
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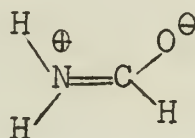
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pyridine. All bond distances and bond angles were determined, and all were based solely on experimentally determined quantities. The accuracy of the bond length measurements was estimated to be  $\pm 0.001 \text{ \AA}$ .

Kurland and Wilson (14) determined the complete structure of formamide and found that the molecule is planar; this was attributed to partial double bond character arising from the contribution of structure II.



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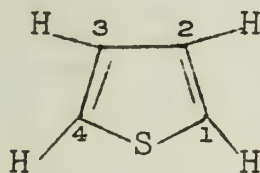
II

The bond lengths were compared with values obtained from x-ray and NMR data on the solid compound:

Microwave

C-O	1.243 $\pm 0.007$ $\text{\AA}$	1.255 $\pm 0.018$ $\text{\AA}$	(x-ray)
C-N	1.343 $\pm 0.007$	1.300 $\pm 0.017$	(x-ray)
N-H	0.995 $\pm 0.007$	1.036 $\pm 0.025$	(NMR)
C-H	1.094 $\pm 0.025$	-	

Five isotopic thiophene molecules were required to determine all bond lengths and angles and to show that the molecule is completely planar (15). The bond lengths obtained by the microwave analysis were compared with those from electron diffraction measurements;



Distance,  $\text{\AA}$

	Microwave	Electron Diffraction
C <sub>2</sub> -H <sub>2</sub>	1.085	1.09
C <sub>3</sub> -H <sub>3</sub>	1.073	1.09
C <sub>2</sub> -S	1.718	1.74 $\pm 0.03$
C <sub>2</sub> -C <sub>3</sub>	1.352	1.35
C <sub>3</sub> -C <sub>4</sub>	1.455	1.44

Probable error in distances was given as  $\pm 0.005 \text{ \AA}$  and in bond angles as  $30'$ . The 2- and 3-deutero, 3,3'-dideutero and tetradeutero compounds were studied in addition to the normal thiophene molecule.

Wilcox and Goldstein (16) studied the pyrrole molecule in the 23-32kmc. region and demonstrated that the molecule is completely planar. Previously there had been some doubt as to whether the N-H bond lay in the plane of the ring. The use of microwave spectroscopy to determine the order of arrangement of the atoms in simple molecules was demonstrated by Beard and Dailey (17), who showed that isothiocyanic acid (HNCS) rather than thiocyanic acid (HSCN) exists in the gas phase. Many other organic molecules have been studied in the microwave region; Townes (18) and Gordy (19) have compiled lists of these molecules and their rotational constants. The literature through 1954 has been included.

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1. *Phragmites australis* (Cav.) Trin. ex Steud.

1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2167, 2168, 2169, 2170, 2171, 2172, 2173, 2174, 2175, 2176, 2177, 2178, 2179, 2180, 2181, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2190, 2191, 2192, 2193, 2194, 2195, 2196, 2197, 2198, 2199, 2200, 2201, 2202, 2203, 2204, 2205, 2206, 2207, 2208, 2209, 2210, 2211, 2212, 2213, 2214, 2215, 2216, 2217, 2218, 2219, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2229, 2230, 2231, 2232, 2233, 2234, 2235, 2236, 2237, 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 2266, 2267, 2268, 2269, 2270, 2271, 2272, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2286, 2287, 2288, 2289, 2290, 2291, 2292, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2301, 2302, 2303, 2304, 2305, 2306, 2307, 2308, 2309, 2310, 2311, 2312, 2313, 2314, 2315, 2316, 2317, 2318, 2319, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2329, 2330, 2331, 2332, 2333, 2334, 2335, 2336, 2337, 2338, 2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 2347, 2348, 2349, 2350, 2351, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2360, 2361, 2362, 2363, 2364, 2365, 2366, 2367, 2368, 2369, 2370, 2371, 2372, 2373, 2374, 2375, 2376, 2377, 2378, 2379, 2380, 2381, 2382, 2383, 2384, 2385, 2386, 2387, 2388, 2389, 2390, 2391, 2392, 2393, 2394, 2395, 2396, 2397, 2398, 2399, 2400, 2401, 2402, 2403, 2404, 2405, 2406, 2407, 2408, 2409, 2410, 2411, 2412, 2413, 2414, 2415, 2416, 2417, 2418, 2419, 2420, 2421, 2422, 2423, 2424, 2425, 2426, 2427, 2428, 2429, 2430, 2431, 2432, 2433, 2434, 2435, 2436, 2437, 2438, 2439, 2440, 2441, 2442, 2443, 2444, 2445, 2446, 2447, 2448, 2449, 2450, 2451, 2452, 2453, 2454, 2455, 2456, 2457, 2458, 2459, 2460, 2461, 2462, 2463, 2464, 2465, 2466, 2467, 2468, 2469, 2470, 2471, 2472, 2473, 2474, 2475, 2476, 2477, 2478, 2479, 2480, 2481, 2482, 2483, 2484, 2485, 2486, 2487, 2488, 2489, 2490, 2491, 2492, 2493, 2494, 2495, 2496, 2497, 2498, 2499, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, 2515, 2516, 2517, 2518, 2519, 2520, 2521, 2522, 2523, 2524, 2525, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2534, 2535, 2536, 2537, 2538, 2539, 2540, 2541, 2542, 2543, 2544, 2545, 2546, 2547, 2548, 2549, 2550, 2551, 2552, 2553, 2554, 2555, 2556, 2557, 2558, 2559, 2560, 2561, 2562, 2563, 2564, 2565, 2566, 2567, 2568, 2569, 2570, 2571, 2572, 2573, 2574, 2575, 2576, 2577, 2578, 2579, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 2606, 2607, 2608, 2609, 2610, 2611, 2612, 2613, 2614, 2615, 2616, 2617, 2618, 2619, 2620, 2621, 2622, 2623, 2624, 2625, 2626, 2627, 2628, 2629, 2630, 2631, 2632, 2633, 2634, 2635, 2636, 2637, 2638, 2639, 2640, 2641, 2642, 2643, 2644, 2645, 2646, 2647, 2648, 2649, 2650, 2651, 2652, 2653, 2654, 2655, 2656, 2657, 2658, 2659, 2660, 2661, 2662, 2663, 2664, 2665, 2666, 2667, 2668, 2669, 2670, 2671, 2672, 2673, 2674, 2675, 2676, 2677, 2678, 26

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*[Faint, illegible handwritten notes]*



## Measurements of Potential Barriers to Internal Rotation

Restricted rotation has been studied in a large number of molecules; in almost all cases the barrier heights have been determined indirectly from thermodynamic measurements. With the advent of microwave spectroscopy, it has become possible to measure barrier heights directly by means of the effects of internal motion on the rotational spectrum of the molecule. In favorable cases the very high resolution and precision of microwave measurements enables these potential barriers to be established with considerably greater accuracy than has previously been possible. Recent studies of the propylene molecule will serve as an example of the method (20). Measurements on the normal species and on  $\text{CH}_3\text{C}^{13}\text{H}=\text{CH}_2$  were made in the 17-36kmc. region. Most of the observed lines were split as a result of internal motion; analysis of these splittings is the basis of the determination of the hindering potential. A method for analyzing splittings has been developed by Hecht and Dennison (21); application of this method to the data on propylene gave an internal potential barrier of  $1978 \pm 17$  cal./mole. The value found by calorimetric measurements is  $1950$  cal./mole.

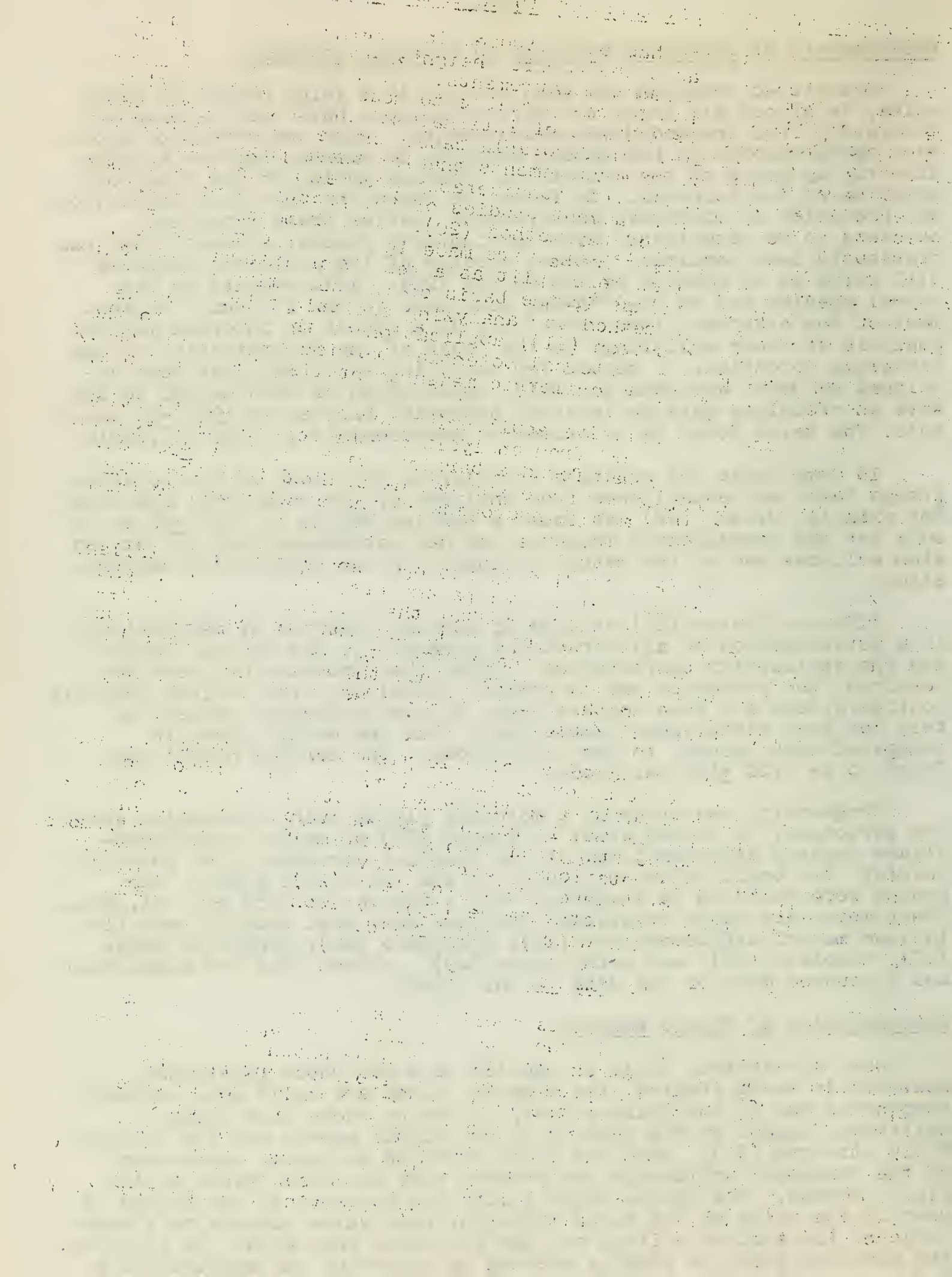
In some cases the relative equilibrium positions of the rotating groups have been established from analysis of the rotational spectrum. For example, Wilson (22) has found a barrier height of  $1150 \pm 50$  cal./mole for the acetaldehyde molecule and has determined that the oxygen atom eclipses one of the methyl hydrogens in the equilibrium conformation.

Kilb and Pierce (23) studied 23 isotopic species of methylsilane in a determination of all structural parameters, the barrier height and the equilibrium conformation. After the structure had been determined, the procedure was to predict transitions for various possible configurations and then compare these with experimental values; in this way they established conclusively that the methyl group is staggered with respect to the silyl group. The barrier height was found to be  $1700 \pm 100$  cal./mole.

Frequently, one study of a molecule yields much information about its structure. A recent study by Pierce (24) of methyl monofluorosilane reports determinations of the complete structure, the potential barrier, the equilibrium configuration and the dipole moment. The groups were found to be staggered with a barrier of  $1559 \pm 30$  cal./mole. Other molecules whose rotational barriers have been studied recently include methyl difluorosilane (25), propylene (26), propylene oxide (27), acrolein (28), and methylamine (29). Wilson (30) has summarized and discussed much of the data in this field.

## Determination of Dipole Moments

When an electric field is applied to a gas whose rotational spectrum is being studied, the observed lines are split into several components due to the Stark effect; it can be shown that these splittings depend on the product of the dipole moment and the electric field strength (31). When the field strength is known, measurement of the frequency splittings can provide very accurate values of the dipole moment. The factor which limits the accuracy of the method is usually the value of the field strength; this value depends on a knowledge of the applied voltage and the electrode separation. In practice, the electric field is usually checked by observing the spectrum of a





molecule such as OCS whose dipole moment is accurately known. The homogeneity of the field is also a limiting factor. Dipole moments as small as 0.1D can be measured with essentially the same accuracy as larger moments, or about 0.2 percent (31). An advantage of this method over the dielectric constant method is that dipole moments can be determined in impure gases since a line of the particular molecule may be singled out for measurement. Since the majority of spectrographs in use are Stark-modulated types, dipole moment measurements are almost always made when a molecule is being studied.

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1. The first part of the report deals with the general situation of the country and the progress of the work during the year. It is a summary of the work done by the various departments and a statement of the results achieved.

2. The second part of the report deals with the work done by the various departments during the year. It is a detailed account of the work done by each department and a statement of the results achieved.

3. The third part of the report deals with the work done by the various departments during the year. It is a detailed account of the work done by each department and a statement of the results achieved.

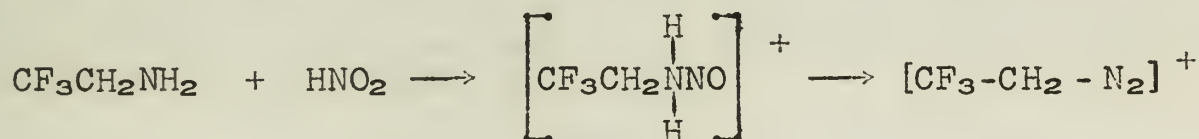
4. The fourth part of the report deals with the work done by the various departments during the year. It is a detailed account of the work done by each department and a statement of the results achieved.

# THE PREPARATION OF DIAZOALKANES

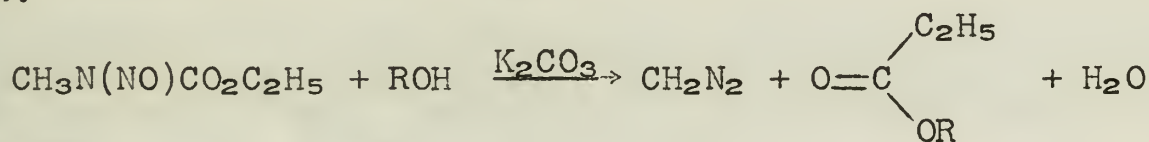
Reported by H. Gruen

November 3, 1958

The general methods for the preparation of diazoalkanes reviewed in part by Gutsche (1) may be summarized as follows: A) The oxidation of hydrazones using mercuric oxide or silver oxide. This method works well for stable di-substituted diazomethanes of the diaryl type. A serious deficiency of the method is the metal-catalyzed decomposition which may compete effectively with the rate of formation in the case of alkyl diazomethanes. B) The action of nitrous acid on amino compounds is useful only in those very few cases (21) where a strongly electron-withdrawing group can stabilize the intermediate ions as indicated below.

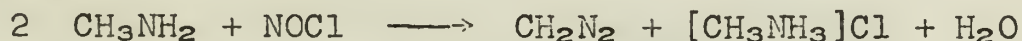


C) The most important method involves the action of base on  $\text{RR}'\text{CHN}(\text{NO})\text{X}$  where X may be  $\text{CONH}_2$ ,  $\text{CO}_2\text{C}_2\text{H}_5$ ,  $\text{CO}\phi$ ,  $\text{C}(\text{CH}_3)_2\text{CH}_2\text{COCH}_3$ ,  $\text{C}(\text{NH})\text{NO}_2$  or  $\text{SO}_2\text{C}_7\text{H}_7$ ; the generalized pattern of the reaction is as shown.

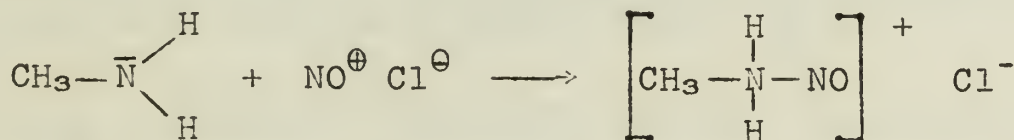


D) Recently two interesting methods for the preparation of diazomethane, capable of extension to other amines, were discovered by Müller and his co-workers (2). The reaction of nitrosyl chloride with methylamine represents the first method (2). Earlier, these workers had examined the interaction of nitrous oxide and methyl-lithium (3) and the effect of nitrosyl chloride on lithium methylamide.

Pertinent aspects of this work and recent applications of method C will be considered in this seminar. Attempts to prepare diazomethane by direct nitrosation of methylamine over the last 70 years were unsuccessful until nitrosyl chloride was combined with excess amine at  $-80^\circ$ .



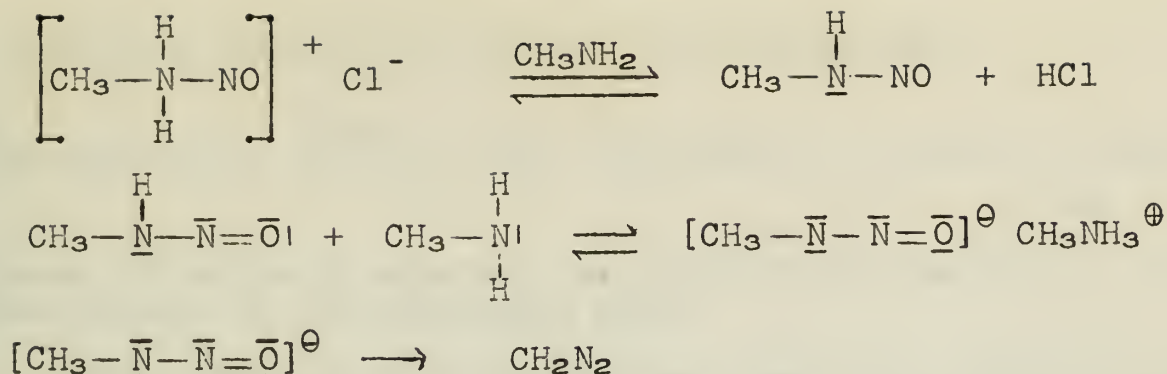
Kinetic investigations by Schmid (4) had shown that alkyl-NHNO  $[\text{alkyl-N}=\text{N}]^\oplus$  were present as short-lived intermediates in the diazotization of aliphatic amines. The mechanism may be represented as shown:



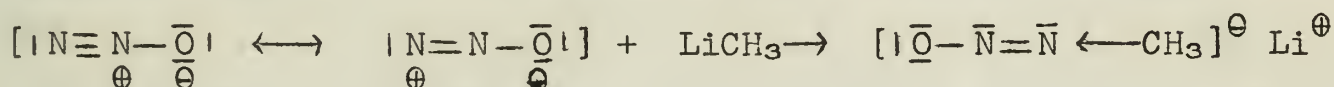
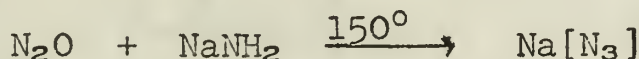
The next steps probably follow the pattern indicated.

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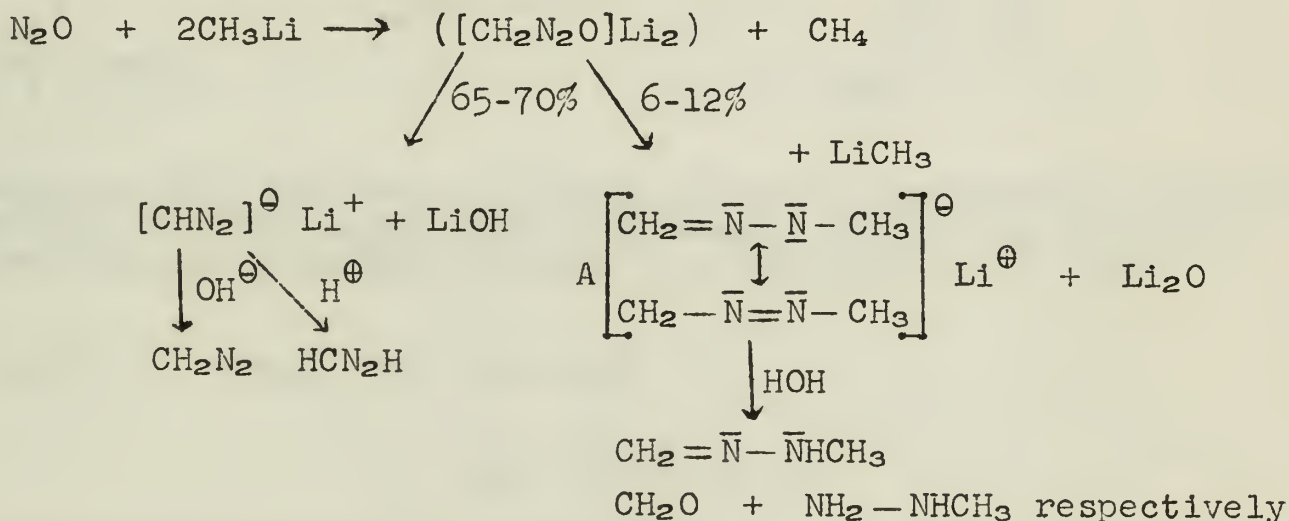


Introduction of  $\text{N}_2\text{O}$  into an ethereal solution of methyllithium yields a precipitate of diazomethyl lithium and lithium hydroxide. Alkaline hydrolysis leads to diazomethane in 70% yield while hydrolysis with potassium dihydrogen phosphate results in formation of the unstable isodiazomethane (3). The first step in the reaction is analogous to the formation of azide.

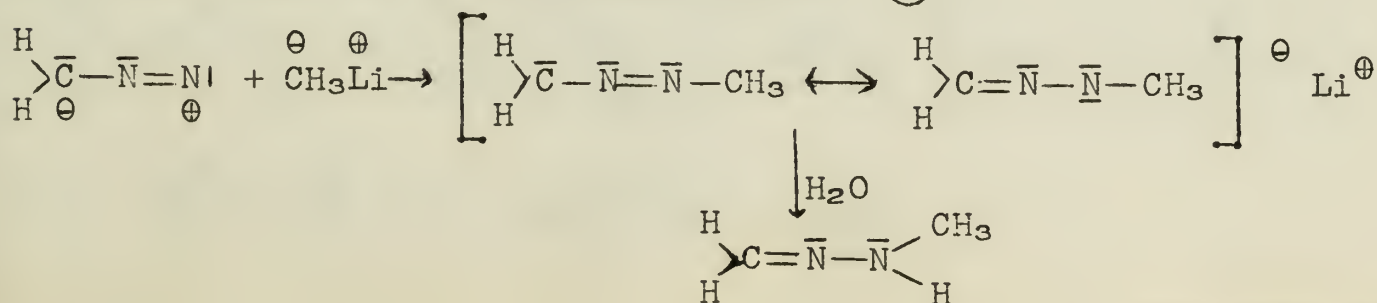


The resonance-stabilized anion could hydrolyze either to methylnitrosamine or methyldiazohydroxide. When this reaction is carried out with labelled  $\text{C}^{14}\text{H}_3\text{Li}$ , only three  $\text{C}^{14}$ -containing products are obtained -  $\text{C}^{14}\text{H}_4$ ,  $\text{C}^{14}\text{H}_2\text{N}_2$  and  $\text{C}_2^{14}\text{H}_6\text{N}_2$ .

The reaction scheme may be indicated as shown:

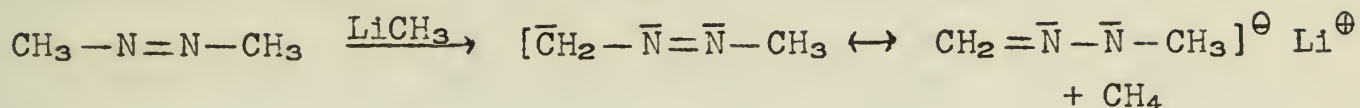


The details of the reaction path leading to diazomethane are not quite certain as yet. The formation of formaldehyde methylhydrazone (5) takes place via the mesomeric anion (A).



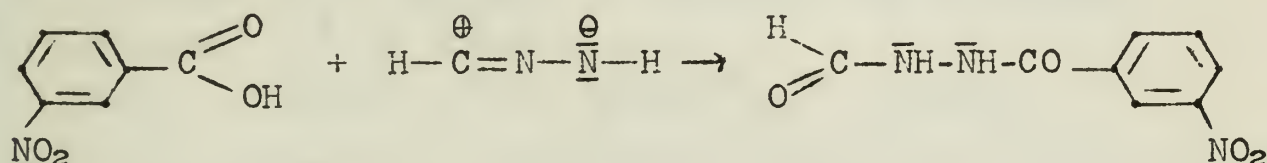


An analogous reaction is observed with azomethane.

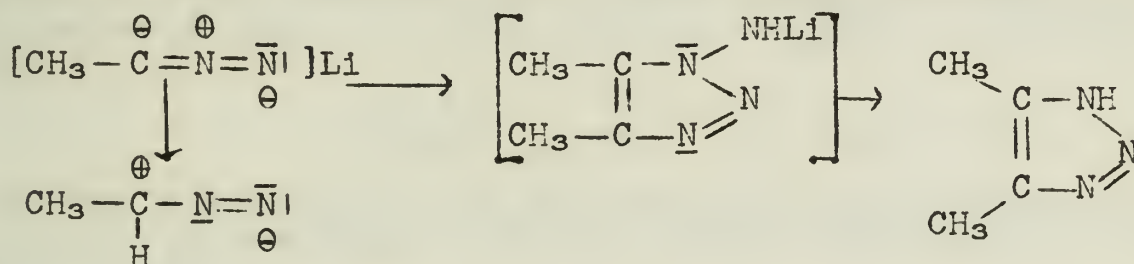


Methane evolution is slow and is probably preceded by a slow rearrangement to the hydrazone form.

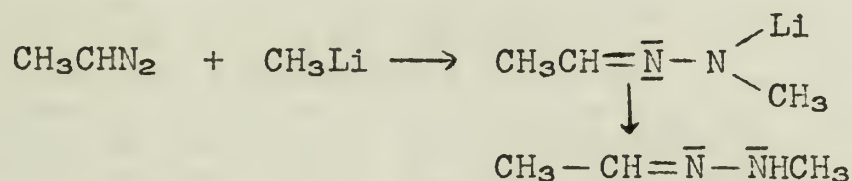
Isodiazomethane was obtained only recently (6); it is an unstable colorless liquid which decomposes violently at room temperature. Its ultraviolet spectrum, with a broad absorption band between 230 and 330 mμ similar to the "azide" band, its ready base-catalyzed conversion to diazomethane and formation of N-formyl-N'-acylhydrazines with organic acids, have served to delineate its structure.



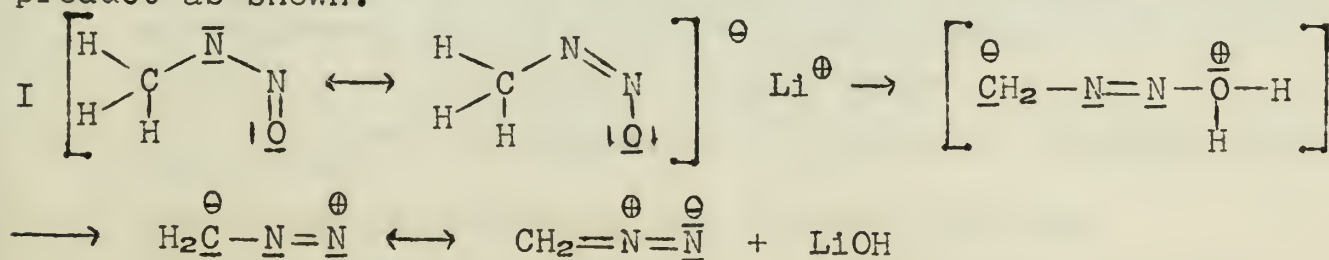
In contrast to the behavior of diazomethane, diazoethane reacts with methyllithium to form 4,5-dimethyl-1,2,3-triazole and acetaldehyde-methylhydrazone; isodiazomethane could not be obtained (7). The course of the reaction is probably as shown.



This competes with addition of methyllithium to diazomethane leading to formation of acetaldehyde methylhydrazone, similar in character to the addition of Grignard reagents to diazoalkanes (22, 23).



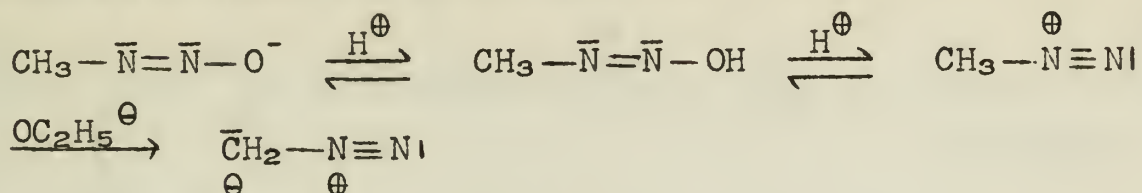
Lithium methylamide reacts with nitrosyl chloride at low temperature to form diazomethane, probably through the intermediacy of methylnitrosamine (3). The anion I may rearrange to the final product as shown.







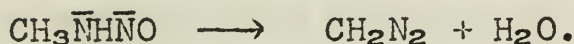
The changes involved in passing from the diazotate anion to the diazoalkane are not quite clear yet. A different scheme has been proposed by Huisgen (8) which is not as convincing as the one above:



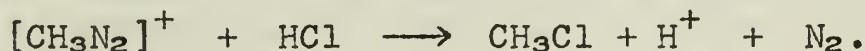
The formation of the methyldiazonium cation as a result of two equilibria is rather unlikely, particularly in a strongly alkaline medium. The mechanism postulated for a base-catalyzed elimination of the diazo hydroxide seems more reasonable. The over-all course of the reaction may be indicated as follows:

- (1)  $[\text{CH}_3\bar{\text{N}}\text{H}]\text{Li} + \text{NOCl} \longrightarrow [\text{CH}_3\bar{\text{N}}\text{H}\bar{\text{N}}\text{O}] + \text{LiCl}$
- (2)  $[\text{CH}_3\bar{\text{N}}\text{H}\bar{\text{N}}\text{O}] + \text{Li}^\oplus[\text{CH}_3\bar{\text{N}}\text{H}]^\ominus \longrightarrow [\text{CH}_3\text{N}_2\text{O}]^\ominus \text{Li}^\oplus + \text{CH}_3\bar{\text{N}}\text{H}_2$
- (3)  $[\text{CH}_3\text{N}_2\text{O}]^\ominus \text{Li}^\oplus \longrightarrow \text{CH}_2\text{N}_2 + \text{LiOH}$
- (4)  $\text{CH}_2\text{N}_2 + [\text{CH}_3\bar{\text{N}}\text{H}]^\ominus \text{Li}^\oplus \longrightarrow [\text{CHN}_2]^\ominus \text{Li}^\oplus + \text{CH}_3\bar{\text{N}}\text{H}_2$

Reaction (2) represents a transmetallation; this could be competitive with



There is independent evidence for occurrence of step (4). The presence of some non-ionic chlorine suggests a side-reaction such as



The easy accessibility of the starting materials and avoidance of unstable intermediates make this method interesting for wider application.

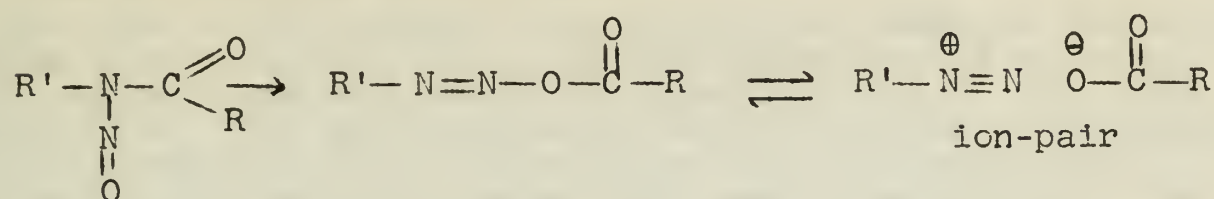
The most general method used for the preparation of diazoalkanes is based on alkaline hydrolysis of N-nitroso compounds as indicated in the introduction. Recent studies in which 3-nitroso-oxazolidones (9,10) and  $\beta$ -substituted nitroso-acylamines (11) were employed showed this decomposition to be quite sensitive to structural and environmental factors. Careful analysis of the experimental requirements recently led to the first satisfactory synthesis of the cyclic diazo compounds-diazocyclohexane (12) and diazocyclobutane (13). The problems involved in the use of N-nitroso compounds may be summarized as follows:

- 1.) Toxicity of the intermediates.
- 2.) Thermal stability during storage and competitive thermal rearrangement during alkaline decomposition.
- 3.) Difficulty of nitrosation of acyl amine.
- 4.) Acid-catalyzed rearrangement of a nitroso-acylamine during nitrosation.
- 5.) Thermal decomposition of diazoalkane generated.
- 6.) Base-catalyzed side reactions of substituted N-nitroso compounds.





The thermal rearrangement of N-nitroso-N-alkyl acylamides has been under extensive investigation (14,15,24); some features of this reaction are now fairly clear.



With R constant, an increase in bulk of R' leads to large increases in rate.

Table (1)

R = C<sub>6</sub>H<sub>5</sub>

<u>R'</u>	<u>k<sub>70</sub> x 10<sup>6</sup> sec<sup>-1</sup></u>
methyl	94.6
isopropyl	44,700.
cyclohexyl	155,000.

Table (2)

R = CH<sub>3</sub>

<u>R</u>	<u>k<sub>70</sub> x 10<sup>6</sup> sec<sup>-1</sup></u>
OEt	.16
NH <sub>2</sub>	71.6
cyclohexyl-	9120.
acetamide	

Steric acceleration in the starting material is the predominating influence (Table (1)). By contrast, electronic influences play a subordinate role not fully evaluated as yet. Hammett sigma-rho relationships have not been examined so far. The effect of variation in R' may be related to the corresponding stabilization of the ground state by resonance; the assumption is made that the transition state is essentially the same in all cases. It is not surprising that the N-cyclohexyl-N-nitroso compounds are all difficult to isolate and very unstable (12). Qualitative observation shows the following order of decomposition rates:

NO-urea < NO-urethane < NO-acetamide << NO-p-toluenesulfonamide

In the N-methyl series, the p-toluenesulfonamide derivative is more stable than the urea derivative. In the secondary alkyl series, in particular, the nitroso group is removed very readily by hydrolysis.

On the basis of qualitative data available, the stability of substituted alkyldiazomethanes decreases rapidly with increasing substitution; Heyns (12) suggests that the +I-inductive effect is important.

Comparison: rearrangement and decomposition rates

	<u>rearrangement rate k(70°)</u>	<u>decomposition rate k(20°)</u>
	<u>nitrosoacetamide</u>	<u>diazalkane</u>

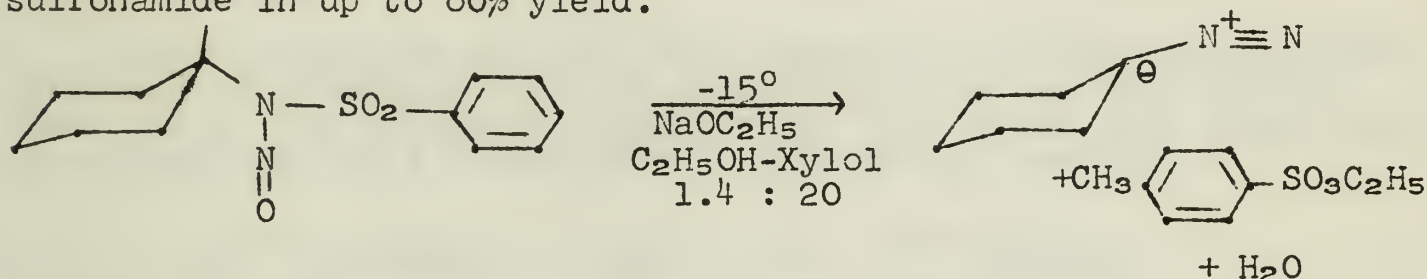
n-butyl	.322 x 10 <sup>-2</sup> min <sup>-1</sup>	2.3 x 10 <sup>-4</sup> min <sup>-1</sup>
cyclohexyl	54.72 x 10 <sup>-2</sup> min <sup>-1</sup>	67.3 x 10 <sup>-4</sup> min <sup>-1</sup>



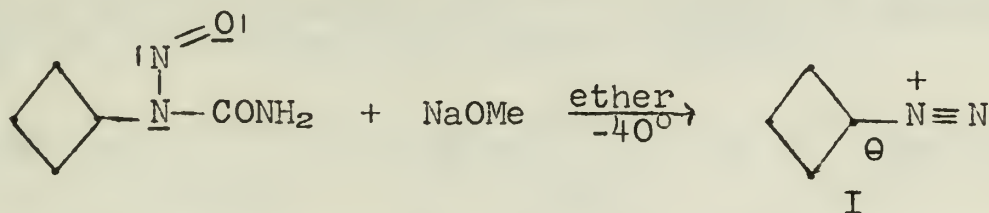
Heyns (12) interprets the analogous increase in rates as indicating the predominance of the electronic effect, but actually this is unwarranted.

The ease of nitrosation is determined by adequate access to the reaction site. Nitrosation of *t*-butyl acylamines is extremely slow, and the nitroso compound cannot be identified due to very fast decomposition. The same applies to the nitrosation of benzhydryl benz- or formamides (14). Nitrosation of *N*-isopropyl- and *N*-cyclohexyl-3-nitroguanidine was also unsuccessful (16). The nature of the acyl component also affects the process by its influence on the electron density at the key nitrogen atom (12).

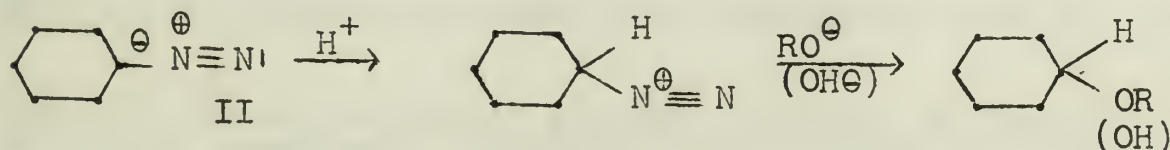
Nitrosation with nitrous gases in glacial acetic acid appears to be the most general method; evidence for significant concurrent acid-catalyzed decomposition is slight. The yields of nitroso compound generally range from 70 to 95% (11, 12, 14), but in the case of cyclohexyl nitroso-urea and -acetamide yields are very low. Diazocyclohexane is best prepared from the *N*-nitroso-*p*-toluene sulfonamide in up to 80% yield.



Diazocyclobutane in solution may be obtained from cyclobutyl nitroso-urea in up to 50% yield as determined by the formation of a mixture of esters of *p*-phenylazobenzoic acid (13).

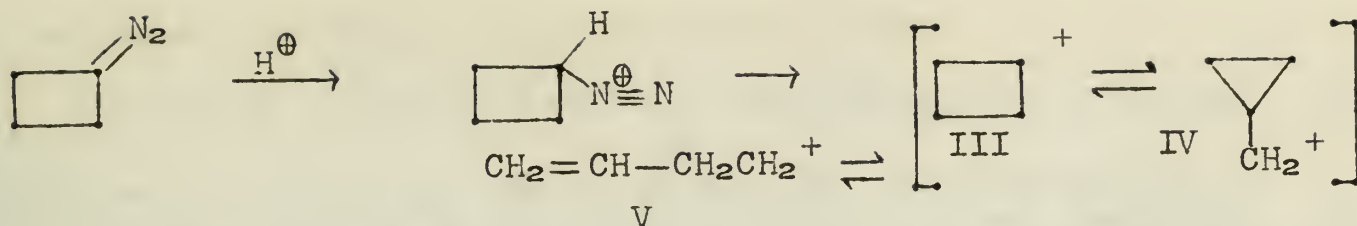


Diazocyclobutane (I) is even less stable than diazocyclohexane (II). The former decomposes within a few minutes at  $-15^\circ$ , but it is stable for several hours at  $-40^\circ$ ; the latter will decompose at a measurable rate at  $20^\circ$ . The nucleophilicity of both compounds is significantly enhanced. Compound II will abstract a proton from ethanol, and I will react with tetrahydrofuran in the presence of acid.

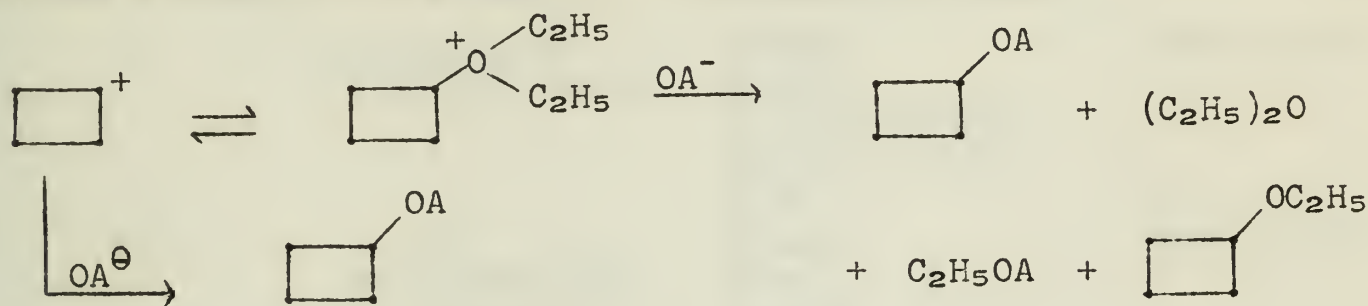




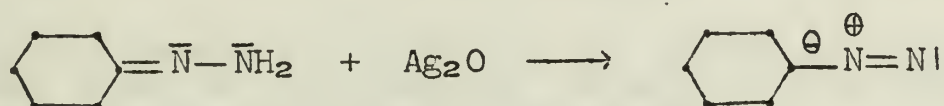




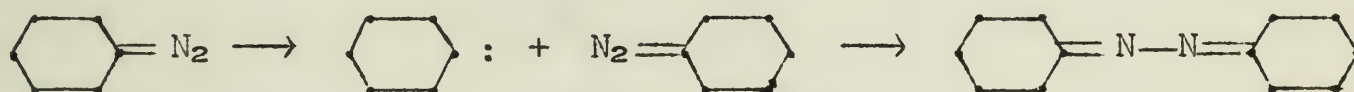
Intermediates III, IV and V or a non-classical ion corresponding to III and IV react further as shown in detail for III.



Diazocyclohexane has also been prepared from the corresponding hydrazone in a maximum yield of 27-28% by oxidation with silver oxide (12). The optimum temperature is  $-15^\circ$ ; above this temperature the silver-catalyzed decomposition proceeds too rapidly.



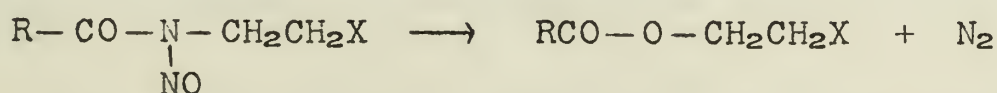
The side reaction leads mainly to the formation of cyclohexylidene azine. Staudinger (17) had shown that ketazines are the principal products of thermal decomposition of secondary diazoalkanes. This decomposition may proceed via carbene formation.



Recently an attempt was made to prepare  $\beta$ -substituted diazoalkanes of the type  $\text{N}_2=\text{CHCH}_2\text{X}$ , where X represents a radical such as  $\text{OCO}\phi$ ,  $\text{OH}$ ,  $\text{Cl}$ ,  $\text{OC}_2\text{H}_5$ ,  $\text{N}(\text{C}_3\text{H}_7)_2$  (11). Only the  $\beta$ -ethoxydiazoethane was obtained by treatment of the appropriate N-nitroso compound with concentrated aqueous methanolic potassium hydroxide. The dinitroso compound  $\phi\text{CO}-\text{N}(\text{NO})-\text{CH}_2-\text{CH}_2-\text{N}(\text{NO})-\text{CO}\phi$  is very stable while

$\phi\text{CO}-\text{N}(\text{NO})-\text{CH}_2\text{CH}_2\text{N}(\text{C}_3\text{H}_7)_2$  cannot be isolated even at  $0^\circ$ . The thermal

lability is significantly greater than that of the non-substituted aliphatic compounds, involving rearrangement and decomposition as shown.



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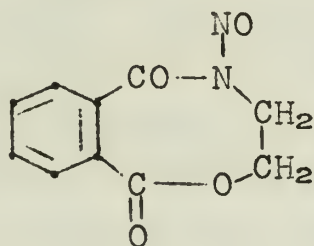


No evidence for radical decomposition is found.

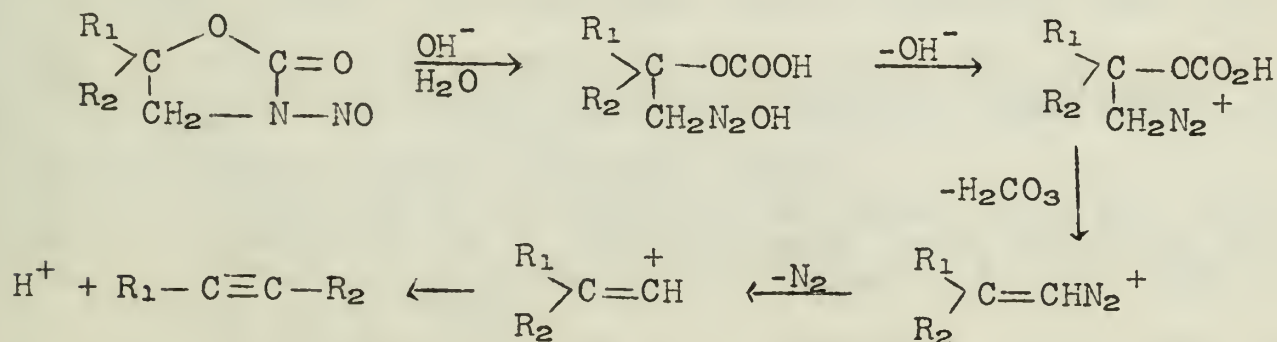
The action of bases on  $\text{O}=\text{C}-\text{N}(\text{NO})-\text{CH}_2\text{CH}_2\text{OCO}\text{O}$  (VI) is striking. Acyl displacement takes place in all cases (18), but the subsequent reactions differ from those of the ordinary nitroso compounds. The nitrosation product obtained from nylon furnishes bis-diazohexane.

Nitroso Compound		Alkali	Reaction Products
A	VI	(19) $\left\{ \begin{array}{l} \text{K}_2\text{CO}_3 \text{ in} \\ \text{CH}_3\text{OH} + \text{phenol} \end{array} \right.$	$\text{O}=\text{C}-\text{O}-\text{CH}_3$ main product $\text{O}=\text{C}-\text{O}-\text{H}$ $\text{O}=\text{C}-\text{O}-\text{CH}_2\text{CH}_2\text{O}-\text{C}-\text{O}$ $\text{CH}_3\text{O}-\text{CH}_2\text{CH}_2\text{O}-\text{C}-\text{O}$ $\text{O}=\text{C}-\text{O}-\text{H}$
B	VI	KOH $\text{H}_2\text{O}:\text{CH}_3\text{OH}=8:3$	$\text{O}=\text{C}-\text{O}-\text{CH}_3$ main product $\text{O}=\text{C}-\text{O}-\text{H}$
C	VI	aniline	$\text{O}=\text{C}-\text{NH}-\text{Ph}$
D	VI	$\text{N}(\text{CH}_3)_3$	$\text{O}=\text{C}-\text{O}-\text{CH}_2\text{CH}_2\text{O}-\text{C}-\text{O}$
E	VII (X=OH)	$\text{K}_2\text{CO}_3$ in acetone	$\text{O}=\text{C}-\text{O}-\text{CH}_2\text{CH}_2\text{O}-\text{C}-\text{O}$ main product $\text{O}=\text{C}-\text{O}-\text{CH}_2\text{CH}_2\text{OH}$ $\text{O}=\text{C}-\text{O}-\text{H}$

In addition, nitrogen and acetylene are always evolved. Gabriel (20) had already observed the formation of acetylene by action of dilute alkali on N-nitroso-O,N-phthaloylaminoethanol.



Newman and his co-workers (9,10) found that 5,5-diaryl 3-nitroso-2-oxazolidones readily gave acetylenes on treatment with base.



If  $\text{R}_1$  and  $\text{R}_2$  are aliphatic the corresponding aldehydes are obtained in good yield.

In the case of the nitroso compounds the yield of acetylenes depends on the base concentrations; beyond .3 Mol./L. aldehydes are obtained; most favorable to acetylene formation are X=O-acyl or



X=OH. The controlled alkaline hydrolysis furnishes a new simple route to alkynes with terminal triple bonds. The starting materials may be either O,N-dibenzoylated or N-monobenzoylated aminoalcohols; the formation of the acetylenes takes place rapidly when the crude nitroso compound is treated with methanolic potassium hydroxide.

	<u>Yield</u>	<u>of</u>	<u>alkynes</u>	<u>-</u>	<u>% of theory</u>
Acetylene	88		Nonyne-1		62
Butyne-1	66		Decyne-1		50
Pentyne-1	51		Phenylacetylene		95
Octyne-1	63				

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# CARBONIUM ION DECOMPOSITION OF ARYL DIAZONIUM SALTS

Reported by J. L. Tveten

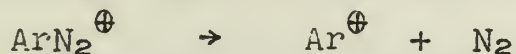
November 10, 1958

## INTRODUCTION

Although reactions involving decompositions of diazonium salts have long been important in organic chemistry, the mechanism of the decomposition has remained subject to speculation. It seems now, however, that the evidence for the intermediacy of the phenyl cation in such decompositions under acidic conditions is considerable. When diazonium salts are allowed to decompose in hydroxylic solvents, the principal, but by no means the only, reaction is:



The mechanism of this reaction appears to involve as the rate determining step the formation of the carbonium ion.



This seminar will deal only with the heterolytic decomposition leading to the aryl carbonium ion, and will include homolytic radical decomposition only for comparison and in order to define the limits of the ionic reaction.

## EVIDENCE FOR HETEROLYTIC DECOMPOSITION

Hausser and Muller (1) were the first to study the rate of decomposition of diazonium salts in water, and, although their data showed inconsistencies, they concluded that the reaction was a unimolecular one. Hantzsch (2) performed a series of experiments similar to those of Hausser and Muller and found that an excess of hydrochloric acid in the reaction mixture had no effect on the rate of reaction of a number of different diazonium salts with water, as measured by the evolution of nitrogen gas. He also confirmed that changing the initial concentration of the salt did not change the magnitude of the velocity constant. However, Hantzsch postulated a mechanism in which the solvent, in this case water, formed an addition complex with the diazonium salt. This then became a syn-diazo compound which in turn decomposed to the final products. It was this mechanism that was accepted for some time.

In 1905, Cain (3) studied the effect of varying the anion on the diazonium salt decomposition in water solution and discovered that for a given diazonium cation ( $\text{ArN}_2^{\oplus}$ ) the rate of nitrogen evolution was the same regardless of whether the anion was chloride, sulfate, nitrate or oxalate. More recent and accurate studies (4,5) have confirmed the independence of rate on the anion in other hydroxylic solvents, and several other anions such as fluoborate and bisulfate were found to fit the same data. These results show that the anion is not involved in the transition state for the decomposition reaction, and thus the reaction does not involve a free radical cleavage to yield phenyl radicals and, for example, chlorine radicals as well as molecular nitrogen.

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Report on the Progress of the Acute Infectious Diseases

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By J. H. Henshaw, M.D., and J. H. Henshaw, Jr., M.D.



Other early work (6) as well as later reports (5) established the fact that as long as the reaction mixture was acidic, addition of further acid had no detectable effect on the reaction rate. Numerous kinetic experiments have been conducted to study the rate of decomposition of the phenyl diazonium salts (5,7-9) as well as the naphthyl analogs (10,11). Although refinements in technique make the more recent reports much more reliable, all the data show excellent agreement with the first-order rate equations. Variations in conditions of the experiments cause discrepancies in the rate constant as obtained by different workers; however, these are in good qualitative agreement, and the results of a given experiment show conclusively that the reaction is unimolecular in its kinetics. The decomposition reaction in the case of the naphthyl series is somewhat complicated by the fact that the diazonium salt may also couple with the naphthol formed as a product of the decomposition. DeTar (11) found that in this case the simple first-order rate expression is applicable only to the first 75-90% of reaction. However, he developed a modified rate expression to allow for the coupling side reaction which yields excellent correlation of the rate data over at least 5-98% reaction.

Pray (12) has also found that the decomposition reaction has a very low solvent sensitivity. He studied the rates of reaction of the diazonium salt with water to yield phenol, with alcohols to give ethers, and with acids to give the corresponding esters. In water-alcohol mixtures, the diazonium compound reacted with either, depending only on the relative amounts of each solvent present. Although the reaction with alcohols occurred somewhat faster than the reaction with water or acids, the relative orders of magnitude were found to be the same, and the rate was nearly independent of the particular alcohol or acid. For example, the diazonium salt reacted at the same rate with methyl alcohol as it did with ethyl or butyl. In like manner the various acids afforded the same pseudo first-order rate constant. In all cases the results agreed well with first-order kinetics. Pray also found no catalyst that would either accelerate or decelerate the decomposition reaction (13). Both ionic salts and colloids were added, with no effect on the rate of nitrogen evolution. The insensitivity to solvent changes would seem to indicate that the mechanism indeed involves a unimolecular formation of the aryl cation rather than solvent displacement of nitrogen from the diazonium cation, although the latter case would appear to give first order kinetics due to the large excess of solvent molecules. Thus the mechanism proposed by Hantzsch may be ruled out under these conditions.

The effects of substituents on the decomposition of diazonium salts are consistent with the unimolecular mechanism. Table I shows the result of placing both electron-attracting and electron-releasing substituents on the ring of benzenediazonium salts. As expected the reaction is accelerated by electron-releasing substituents in the meta position and retarded by electron-attracting substituents. However, although electron-attracting para-substituents ( $\text{NO}_2$ , etc.) decelerate the reaction as one would expect, so do electron-furnishing ones. Hughes has suggested that this deactivation can be regarded as consistent with the  $\text{S}_{\text{N}}1$  mechanism since these groups stabilize, through resonance, the diazonium ion more than the transition state (14).





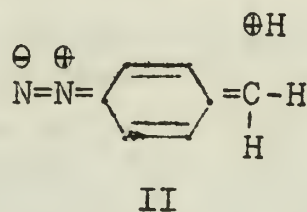
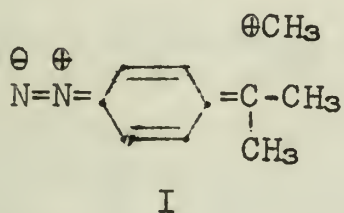
Table I

Effect of substituents on the rate of decomposition of benzenediazonium salts at 28.8° C.

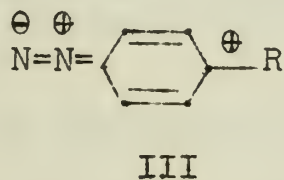
Rate coefficient ( $\text{sec}^{-1} \times 10^7$ )

Substituent	Ortho	Meta	Para
-OH	6.8	9100	0.93
-OCH <sub>3</sub>		3400	0.11
-C <sub>6</sub> H <sub>5</sub>	1100	1700	37
-CH <sub>3</sub>	3700	3400	91
-H	740	740	740
-COOH	140	410	91
-SO <sub>3</sub> <sup>-</sup>	91	150	42
-Cl	0.14	31	1.4
-NO <sub>2</sub>	0.37	0.69	3.1

Lewis (15) has studied the effect of structure of alkyl groups on the rate of decomposition of alkyl substituted benzenediazonium salts. For both the meta- and para-substituted compounds the general order t-butyl faster than methyl was observed. It is evident that there can be several effects operative; inductive, resonance and solvent. The t-butyl group has a slightly greater inductive effect than the methyl as shown by the dipole moment of t-butylbenzene, which is greater than that of toluene (16). Thus this group has a greater ability to neutralize the positive charge developed on the ring during the formation of the phenyl carbonium ion, and the decomposition rate is increased. This would be the chief effect operative in the meta-substituted case, and thus the difference in rate can be thought of as due largely to the increased inductive effect of the t-butyl. For the para-substituted diazonium salt, however, the resonance effects must also be considered. Lewis suggests that structures such as I with no-bond to carbon are less important than those with no-bond to hydrogen, as in II.



Recent work of Schubert (17), however, indicates that this is not the case. The source of the effect seems to be steric hindrance to solvation of electron-deficient sites near the alkyl substituent rather than C-H versus C-C hyperconjugation. Thus, for resonance structures such as III, a large alkyl group R hinders solvation of the positive charge on the ring and results in destabilization of the diazonium ion.



Whatever the cause, the rate-decreasing resonance of the diazonium ion becomes less important as the  $\alpha$ -carbon atom becomes more highly sub-

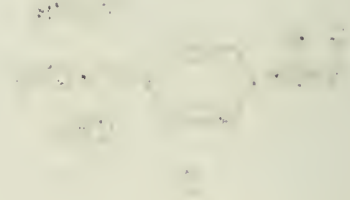


# Report of the Committee on the Administration of the Government of the District of Columbia

Submitted to the Senate and House of Representatives

Year	Amount	Per Cent
1901	1,000,000	100
1902	1,100,000	110
1903	1,200,000	120
1904	1,300,000	130
1905	1,400,000	140
1906	1,500,000	150
1907	1,600,000	160
1908	1,700,000	170
1909	1,800,000	180
1910	1,900,000	190
1911	2,000,000	200
1912	2,100,000	210
1913	2,200,000	220
1914	2,300,000	230
1915	2,400,000	240
1916	2,500,000	250
1917	2,600,000	260
1918	2,700,000	270
1919	2,800,000	280
1920	2,900,000	290
1921	3,000,000	300
1922	3,100,000	310
1923	3,200,000	320
1924	3,300,000	330
1925	3,400,000	340
1926	3,500,000	350
1927	3,600,000	360
1928	3,700,000	370
1929	3,800,000	380
1930	3,900,000	390
1931	4,000,000	400
1932	4,100,000	410
1933	4,200,000	420
1934	4,300,000	430
1935	4,400,000	440
1936	4,500,000	450
1937	4,600,000	460
1938	4,700,000	470
1939	4,800,000	480
1940	4,900,000	490
1941	5,000,000	500
1942	5,100,000	510
1943	5,200,000	520
1944	5,300,000	530
1945	5,400,000	540
1946	5,500,000	550
1947	5,600,000	560
1948	5,700,000	570
1949	5,800,000	580
1950	5,900,000	590
1951	6,000,000	600
1952	6,100,000	610
1953	6,200,000	620
1954	6,300,000	630
1955	6,400,000	640
1956	6,500,000	650
1957	6,600,000	660
1958	6,700,000	670
1959	6,800,000	680
1960	6,900,000	690
1961	7,000,000	700
1962	7,100,000	710
1963	7,200,000	720
1964	7,300,000	730
1965	7,400,000	740
1966	7,500,000	750
1967	7,600,000	760
1968	7,700,000	770
1969	7,800,000	780
1970	7,900,000	790
1971	8,000,000	800
1972	8,100,000	810
1973	8,200,000	820
1974	8,300,000	830
1975	8,400,000	840
1976	8,500,000	850
1977	8,600,000	860
1978	8,700,000	870
1979	8,800,000	880
1980	8,900,000	890
1981	9,000,000	900
1982	9,100,000	910
1983	9,200,000	920
1984	9,300,000	930
1985	9,400,000	940
1986	9,500,000	950
1987	9,600,000	960
1988	9,700,000	970
1989	9,800,000	980
1990	9,900,000	990
1991	10,000,000	1000

The Committee on the Administration of the Government of the District of Columbia has the honor to submit to the Senate and House of Representatives this report on the administration of the District of Columbia for the year 1991. The report is divided into two parts: a general statement of the administration and a detailed statement of the accounts. The general statement is divided into three sections: a statement of the general administration, a statement of the administration of the District of Columbia, and a statement of the administration of the District of Columbia. The detailed statement of the accounts is divided into two parts: a statement of the accounts of the District of Columbia and a statement of the accounts of the District of Columbia. The Committee has the honor to submit this report to the Senate and House of Representatives in accordance with the provisions of the District of Columbia Organic Act of 1800, as amended.

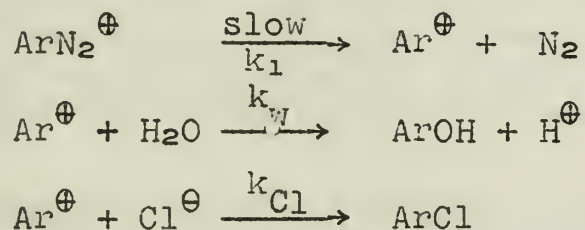


The Committee on the Administration of the Government of the District of Columbia has the honor to submit to the Senate and House of Representatives this report on the administration of the District of Columbia for the year 1991. The report is divided into two parts: a general statement of the administration and a detailed statement of the accounts. The general statement is divided into three sections: a statement of the general administration, a statement of the administration of the District of Columbia, and a statement of the administration of the District of Columbia. The detailed statement of the accounts is divided into two parts: a statement of the accounts of the District of Columbia and a statement of the accounts of the District of Columbia. The Committee has the honor to submit this report to the Senate and House of Representatives in accordance with the provisions of the District of Columbia Organic Act of 1800, as amended.

stituted. This effect is in the same direction as the inductive effect already mentioned, and thus the para-substituted compound is also more reactive with the t-butyl group.

## SELECTIVITY OF THE PHENYL CATION

The preceding evidence has been put forth to support the hypothesis that the decomposition of aryl diazonium salts in acid media goes through a carbonium ion intermediate. Quite recently Lewis (18) has made a study of the reactivity of this carbonium ion by looking at the formation of chlorobenzene and phenol from the decomposition of benzenediazonium fluoborate in aqueous chloride solutions. This work not only serves to study the reactivity of the very unstable phenyl cation, but also helps to confirm the mechanism. The assumed mechanism may be represented by:



The yields of phenol ( $Y_{\text{ArOH}}$ ) and chlorobenzene ( $Y_{\text{ArCl}}$ ) can be related by the following equation.

$$\frac{Y_{\text{ArCl}}}{Y_{\text{ArOH}}} = \frac{k_{\text{Cl}} (\text{Cl}^{\ominus})}{k_w (\text{H}_2\text{O})}$$

The ratio  $k_{\text{Cl}}/k_w$  is called the competition factor for the chloride ion. The fact that this competition factor was found to remain relatively constant seems to confirm the carbonium ion mechanism. It is not complete proof, but taken together with the other evidence there can be little doubt of the course of the reaction.

For a wide range of chloride ion concentrations, using both hydrochloric acid and sodium chloride, Lewis found that the ratio  $k_{\text{Cl}}/k_w$  was consistently about 3. This checks quite well in order of magnitude with calculations made using other kinetic data available in the literature. To illustrate the high reactivity of the phenyl cation as evidenced by these data, it is interesting to compare the results with competition factors between chloride ion and water for more stable carbonium ions. Swain (19) gives from various sources for the trityl cation, the benzhydryl cation and the t-butyl cation the values 3000, 600 and 180, respectively. Thus it may be seen that the value of 3 obtained for the phenyl cation indicates that it is very reactive and thus possesses low selectivity in its reactions. There are numerous other indications of this reactivity in the literature, but they are summarized in the article by Lewis (18) and will not be mentioned in detail here.

## REACTIONS OF DIAZONIUM SALTS

The products, as well as the kinetics, of the diazonium decomposition indicate that in acidic solution the unimolecular formation of the aromatic cation is the rate controlling step. In addition to the

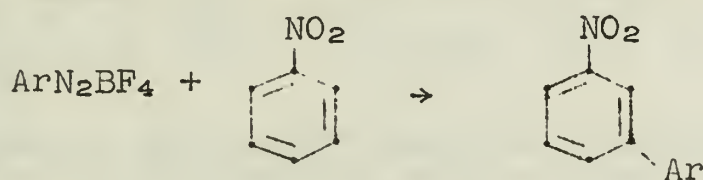




reactions with water, alcohols and acids to yield phenols, ethers and esters, respectively, there are numerous other reactions of interest from a mechanistic viewpoint. First it should be pointed out that the heterolytic decomposition occurs only in acidic or originally neutral solutions, while in basic or buffered media it seems likely that the reaction is radical in nature.

DeTar (20-22) has found that, although the principal product of the thermal decomposition of benzenediazonium fluoborate or chloride in methanol under acidic conditions is anisole (93%), with acetate buffers the reaction is much more complex. Under these conditions some anisole is produced, but the main product is benzene; smaller amounts of biphenyl and traces of azobenzene are also formed. Oxygen has a very pronounced effect on the reaction, causing the product mixture to be dark brown in color with only 30-75% of the theoretical amount of nitrogen being evolved. This reaction is almost certainly a free radical one, involving first the formation of a diazo compound with the base or buffer anion followed by homolytic cleavage to give the phenyl radical. DeTar has extensively investigated the kinetics of the radical reaction.

The decomposition of aryldiazonium fluoborates in solutions of benzene derivatives substituted with meta-orienting groups has been studied by Nesmeyanov (23). Homolytic decomposition of the diazonium fluoborate would be expected to lead to the entering of the aryl radical at the ortho- and para-positions of the benzene ring. If the decomposition occurs heterolytically, however, the resulting aryl cation should attack the ring primarily in the meta-position to the meta-orienting group. Although the yields of products obtained from the phenylation of the aromatic nucleus were often fairly low, there was, nevertheless, a large predominance of meta-substitution. For example, when aryldiazonium fluoborates were decomposed in nitrobenzene the product was found to be 90% of that in which the aryl group occupied the meta-position to the nitro group.



Similar decompositions in benzene derivatives substituted by quaternary ammonium, carbalkoxy, trifluoromethyl and acetyl groups also led predominantly to meta-substituted biaryls. Thus there can be little doubt that the attacking species is the aryl cation.

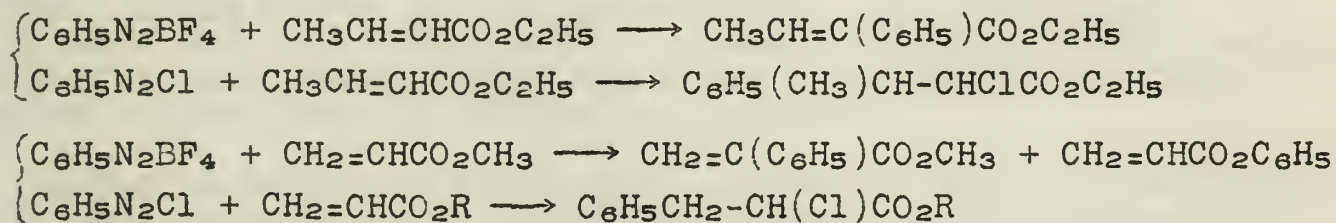
Decomposition of benzenediazonium fluoborate in a nitrile medium leads to the addition of the phenyl to nitrogen (24), and hydrolysis of the resulting nitrilium fluoborate affords an anilide of the corresponding acid in fair yield. Similar results were obtained (25) by decomposing benzenediazonium fluorosilicate, thus excluding any specific role of boron trifluoride.

By reacting various diazonium salts with carbon-carbon double bonds, Nesmeyanov (26) has shown that in non-hydroxylic solvents the anion of the diazonium salt may affect the mechanism of the decomposition. In good solvents under acidic conditions the reaction goes readily through the carbonium ion, and the rate is independent of the anion involved. In other cases, however, the entire course of reaction



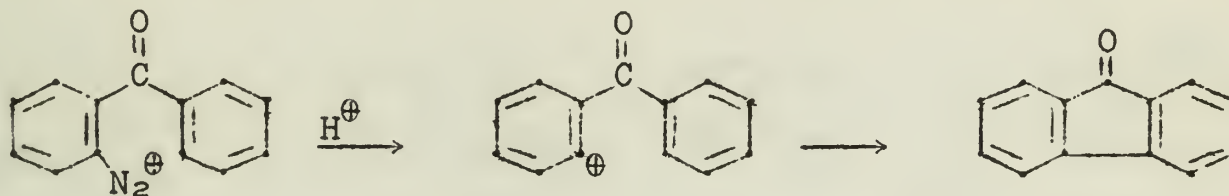


may be changed by using chloride instead of fluoborate. This may be explained by the fact that the chloride may exist partially as the covalent diazochloride, and homolytic cleavage results in the phenyl and chlorine radicals which, although not very stable, do not have prohibitive energy requirements. The fluoborate, on the other hand, has no such covalent form, and homolytic cleavage does not occur. Thus it is that the reactions of the two salts differ under non-ideal reaction conditions. The position of phenyl attack on double bonds shows this divergence clearly. The decomposition of benzenediazonium fluoborate in ethyl crotonate results in phenylation at the  $\alpha$ -position to the ethoxycarbonyl group to yield (after saponification) methyl-atropic acid. The decomposition of benzenediazonium chloride, on the other hand, leads to phenyl occupying the  $\beta$ -position, to form  $\alpha$ -chloro- $\beta$ -phenylisobutyric acid. Similar results have been obtained for other double-bond compounds.



## INTRAMOLECULAR REACTIONS

Ring closure reactions involving the diazonium group have likewise been shown to go by way of the aryl carbonium ion under acidic conditions. For example, DeTar (27) has studied the decomposition of the diazonium salt from 2-aminobenzophenone in acid and found that the reaction yields fluorenone in high yields. Similar decompositions

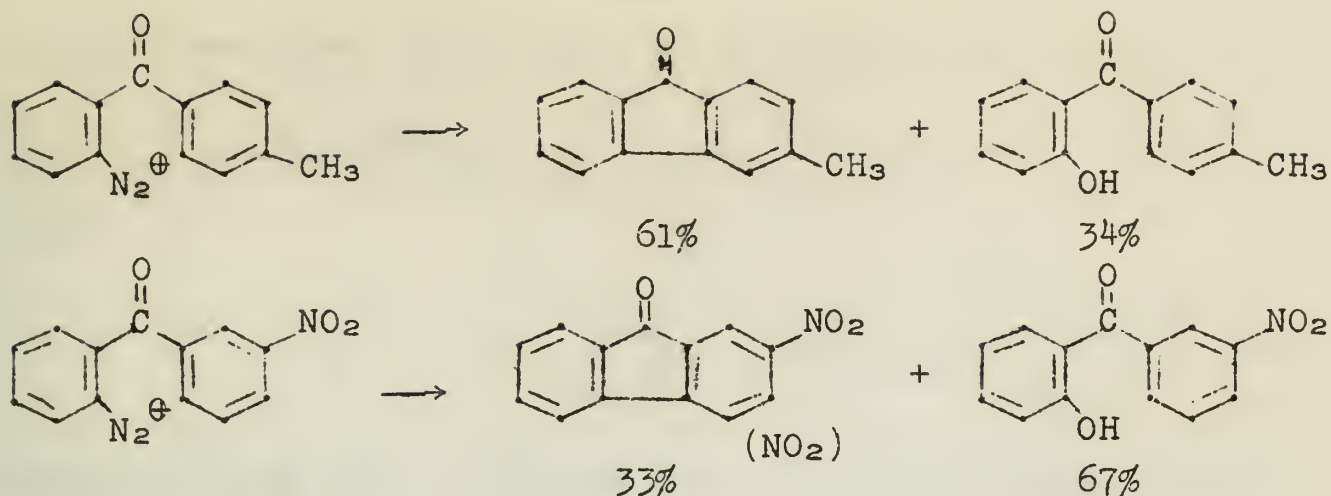


in base, however, gave only traces of fluorenone. Increasing acid concentration in the reaction mixture leads to slightly higher yields of the cyclization product and less phenolic by-product (28). This may be explained by the fact that there is less water present to react in the phenol-forming side reaction.

The heterolytic decomposition mechanism may be further verified in the fluorenone ring closure reaction by investigating the effect of appropriately substituted benzophenones (29). The thermal decomposition of the diazonium salt derived from 2-aminobenzophenone in aqueous solution gave 65% of fluorenone and 35% of 2-hydroxybenzophenone, the two products accounting quantitatively for the starting material. These products may be attributed to competing reactions of the carbonium ion. Since a methyl group activates and a nitro group deactivates an aromatic ring toward attack by the phenyl cation, the methyl group should increase and the nitro group should decrease the yield of fluorenone in the ionic reaction. However, the nitro group increases the reactivity of the ring toward radical attack, and if a homolytic decomposition takes place the relative yield of fluorenone would be increased.

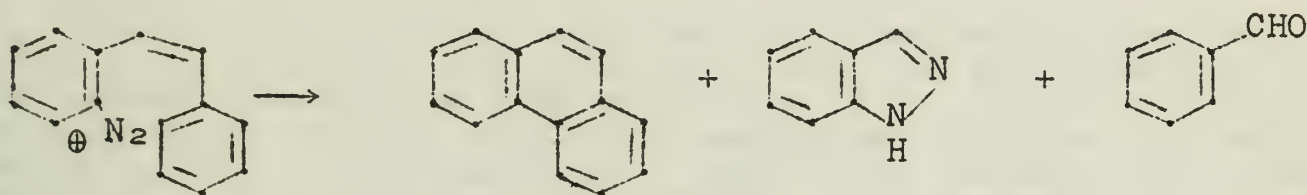




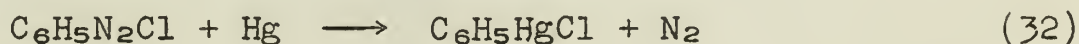


The yields given in the equations show that although the methyl group has very little effect on the product ratio, the nitro group deactivates the ring sufficiently to cause a decrease in the relative amount of ring closure. Again the facts indicate a heterolytic reaction rather than the homolytic alternative.

Another slightly different form of the cyclization reaction is the thermal decomposition of cis-2-stilbenediazonium fluoborate in dilute acid, leading to 15-40% yields of phenanthrene and 60-70% yields of a cleavage product, indazole, depending on the temperature (30). DeTar has postulated the mechanism of the indazole formation as electrophilic attack of the terminal nitrogen at the ethylenic bond followed by addition of water to give the protonated 3-( $\alpha$ -hydroxybenzyl)-indazole. After transfer of the proton to the nitrogen atom this can undergo a reverse aldol cleavage to yield indazole and protonated benzaldehyde.



The amount of phenanthrene afforded by the above reaction has been found to be greatly increased by the addition of copper powder to the reaction mixture. In this case the rate is also measurably increased. This effect has been noted in the Pschorr synthesis and many related reactions (31). Although the mechanism of this copper catalysis is still in question, there is evidence that homolytic decomposition is invoked. It is probable that the decomposition is similar to that of diazonium salts with certain metals to yield the organometallic compound.

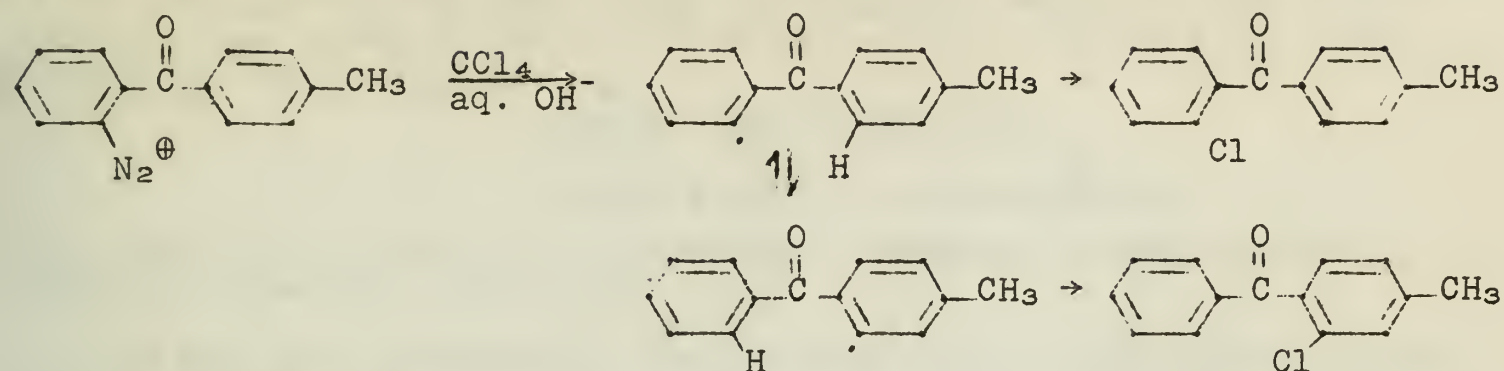


An interesting example of the effect of replacing the acidic reaction conditions with alkaline ones is shown in the decomposition of 2-(4'-methylbenzoyl)-benzenediazonium salts in basic solution (33). As was stated before, the reaction in acid yields the substituted fluorenone and phenol; however, in carbon tetrachloride/aqueous hydroxide the products are two isomeric chloro compounds. In this case it is necessary to postulate a radical decomposition followed





by hydrogen transfer. From this reaction it is also possible to obtain

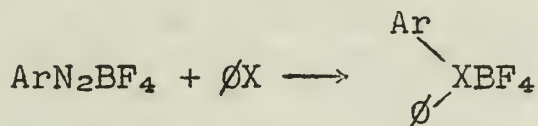


information on the ease of abstraction of halogen from halogenated methane derivatives.

## DIARYLHALONIUM SALTS

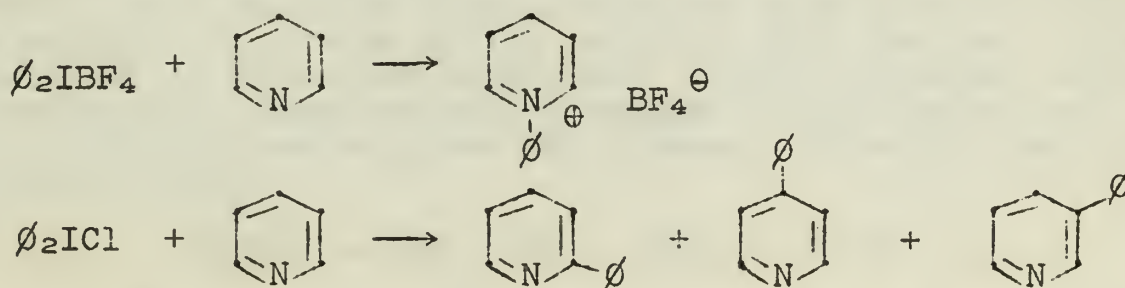
The subject of diarylhalonium salts has been covered in a recent University of Illinois seminar (34). Since that time, however, there have been several noteworthy experiments conducted, especially with the diphenylbromonium and diphenylchloronium compounds. These are made by use of the corresponding diazonium salt, and exhibit many of the properties of diazonium salts on decomposition.

Nesmeyanov and co-workers (35) have reported improved yields, increased from 1% to 5%, of the bromonium and chloronium salts by the action of the diazonium fluoborate on the corresponding halobenzene.



It is interesting to note that the three halonium salts; iodide, bromide and chloride, all react similarly and are excellent phenylating agents; however, in this case, as with the diazonium salts in nonhydroxylic solvents, the anion associated with the compound has a marked effect on its reactivity. Thus either heterolytic or homolytic phenylation can be achieved by the use of the halonium fluoborates or halides respectively.

An example is the phenylation of pyridine with diphenyliodonium salts (26); the fluoborate yielding the N-phenylpyridinium salt in 88% yield, while the chloride gives a mixture of products of phenylation on carbon.

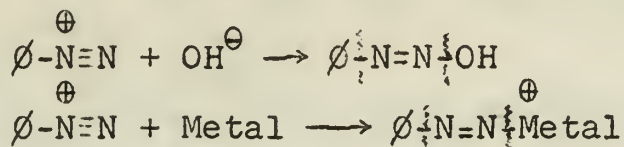


The same effect may be seen in other reactions as well; thus while the halonium halides react with metallic mercury to form the organomercurial, the fluoborate salts do not undergo this reaction. However, the situation is just the opposite with metallic thallium; a diphenylthallium salt is formed only from the fluoborates. Nesmeyanov (35) has suggested a possible reason for these anomalies,





relating the halonium case to similar results in the diazonium series. It is proposed that metals, being nucleophylic reagents, can, like hydroxyl ion, convert the diazonium cation into a diazo form which decomposes homolytically.

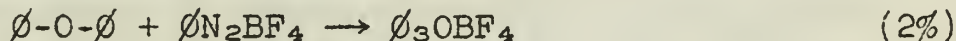


This would also account for the effect of copper in ring closure reactions discussed previously.

An analogous explanation for halonium salts would require a transition complex with the metal in which the diphenylhalonium cation is in a covalent form (with a 10-electron shell). Mercury, which is sufficiently nucleophylic to bring about transformation of the diazonium into the diazo form, cannot accomplish this with the diphenylhalonium ions, and only the halonium halides, in which assistance is given by the halide, will react. The less noble metals such as thallium can bring about this transformation with the more ionic fluoborate, and the covalent halide serves only to hinder the attack.

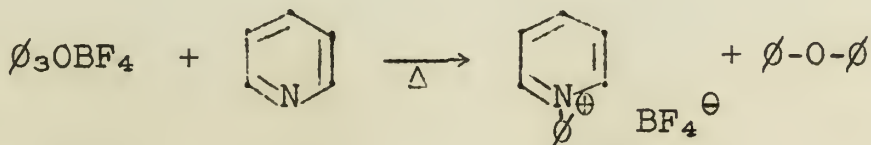
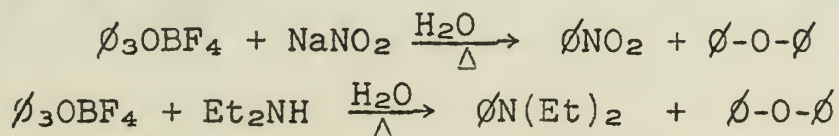
### TRIPHENYLOXONIUM SALTS

Nesmeyanov (36) has recently reported the preparation of triphenyloxonium salts, a type of compound which was previously unknown, from the reaction of benzenediazonium fluoborate with diphenyl ether. Unlike the trialkyloxonium salts of Meerwein (37,38), the triaryl analogs are stable compounds with decomposition temperatures above 150°C. Most of them are only difficultly soluble in water. The triphenyloxonium compound was synthesized as the fluoborate salt, and salts with other anions may be obtained from the product. In this way a wide variety of salts have been prepared.



In contrast to the alkyloxonium salts and to the diarylhalonium salts previously mentioned, the triphenyloxonium salts enter very sluggishly into phenylation reactions. Thus triphenyloxonium chloride, bromide, iodide and fluoborate do not, under any conditions tested, phenylate metallic mercury, and the fluoborate does not react with copper or thallium. This inertness towards metals may be explained by the inability of oxygen to expand its octet to ten electrons, as has been previously mentioned in the case of the halonium salts.

Phenylation of such anions as nitrite and azide, reactions which proceed readily with halonium salts, requires many hours of refluxing in aqueous solution to obtain yields of about 25%; the rest of the starting material is recovered unreacted. Amines, however, react more readily. Pyridine is phenylated at nitrogen in 90% yield, and phenylation of diethyl amine gives 60% product, although the reaction proceeds only in water.







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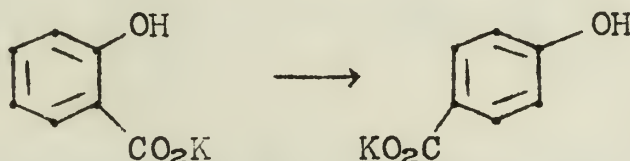
# CARBOXYLATE REARRANGEMENTS IN AROMATIC SYSTEMS-- A NEW SYNTHETIC ROUTE TO AROMATIC ACIDS

Reported by J. Diekmann

November 17, 1958

## INTRODUCTION

The rearrangement of carboxylate groups in aromatic systems was observed as early as 1873 by Wislicenus, who obtained small amounts of isophthalate and terephthalate when he heated sodium benzoate at elevated temperatures (1). Probably the best known example of such a carboxylate rearrangement was provided by Kolbe in his salicylic acid synthesis. He found that potassium *o*-hydroxybenzoate, on heating, rearranged to yield the para isomer (2):

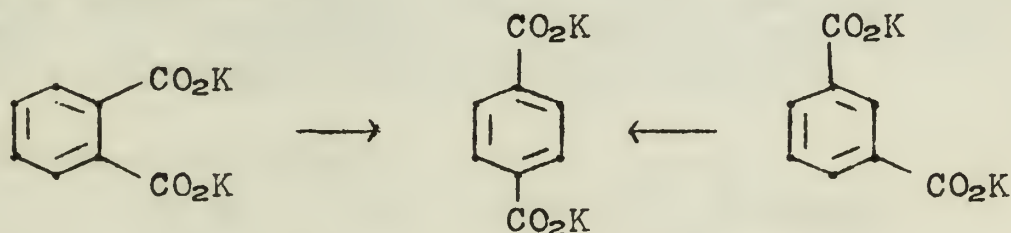


While these reports have been confirmed by independent workers (3,4), no additional information was published until recently when commercial interest in the production of terephthalic acid prompted a reinvestigation of the conditions of such a rearrangement. This seminar will be concerned with a discussion of the recent findings.

## SCOPE OF THE REACTION

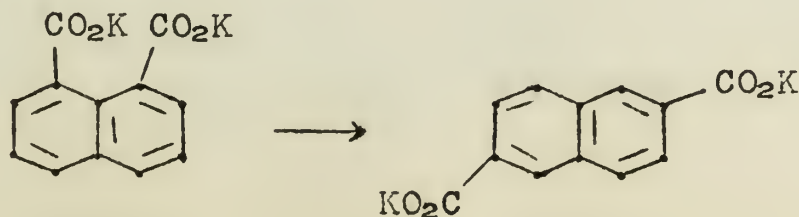
### Alicyclic Aromatic Systems:

The first compound to be investigated by Raecke (5), the discoverer of the general nature of this reaction, was dipotassium *o*-phthalate. Raecke found that, at elevated temperatures, he was able to obtain a substantial yield of dipotassium terephthalate. Dipotassium isophthalate also rearranges under these conditions to yield the terephthalate:



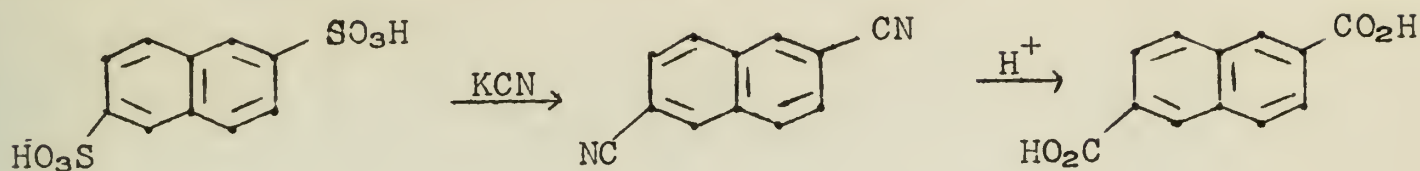
Similarly, one can also employ phthalic anhydride and an equimolar amount of potassium carbonate to arrive at the terephthalate under these conditions (6).

An analogous reaction can be found in the naphthalene series. Dipotassium 1,8-naphthalenecarboxylate rearranges to give the 2,6-dicarboxylate (7):

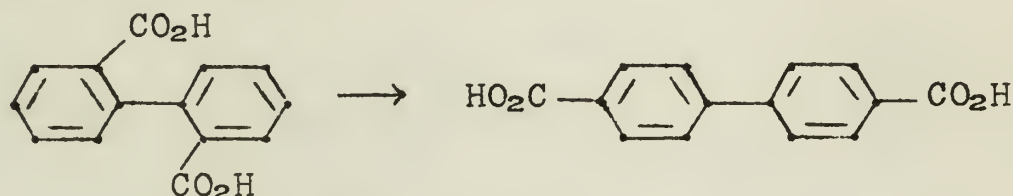




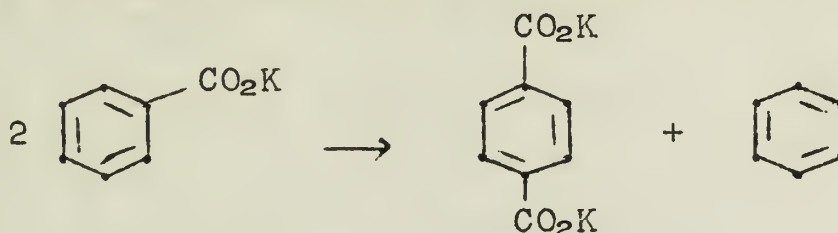
Previously it had been difficult to synthesize this acid. An alternative route is shown below (8):



The dipotassium salt of diphenic acid undergoes a similar rearrangement. The product is the 4,4'-diphenylcarboxylate. An earlier synthetic route to this acid was the oxidation of di-p-tolyl with dichromate.



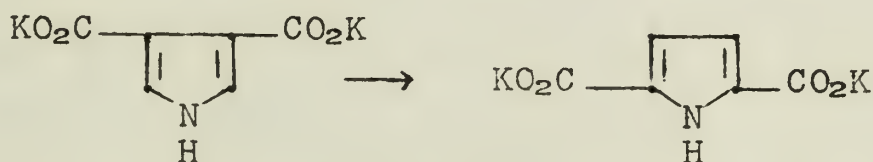
When potassium benzoate was heated at high temperatures, again dipotassium terephthalate and benzene were obtained.



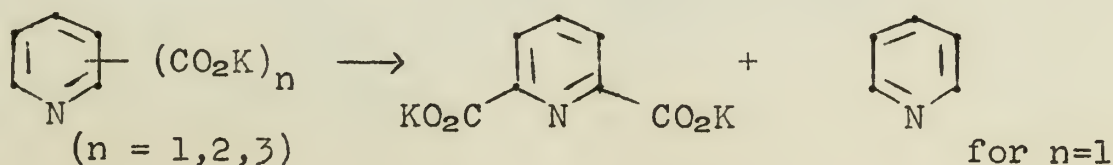
This disproportionation reaction also has an analogy in the naphthalene series, where either  $\alpha$ - or  $\beta$ -potassium naphthoate yields 2,6-dipotassium naphthalenedicarboxylate.

## HETEROCYCLIC AROMATIC SYSTEMS

Carboxylate ion migration also appears to be quite general in heterocyclic aromatic systems, where milder reaction conditions can be employed (5). Dipotassium 3,4-pyrrolicarboxylate, for example, rearranges to dipotassium 2,5-pyrrolicarboxylate:



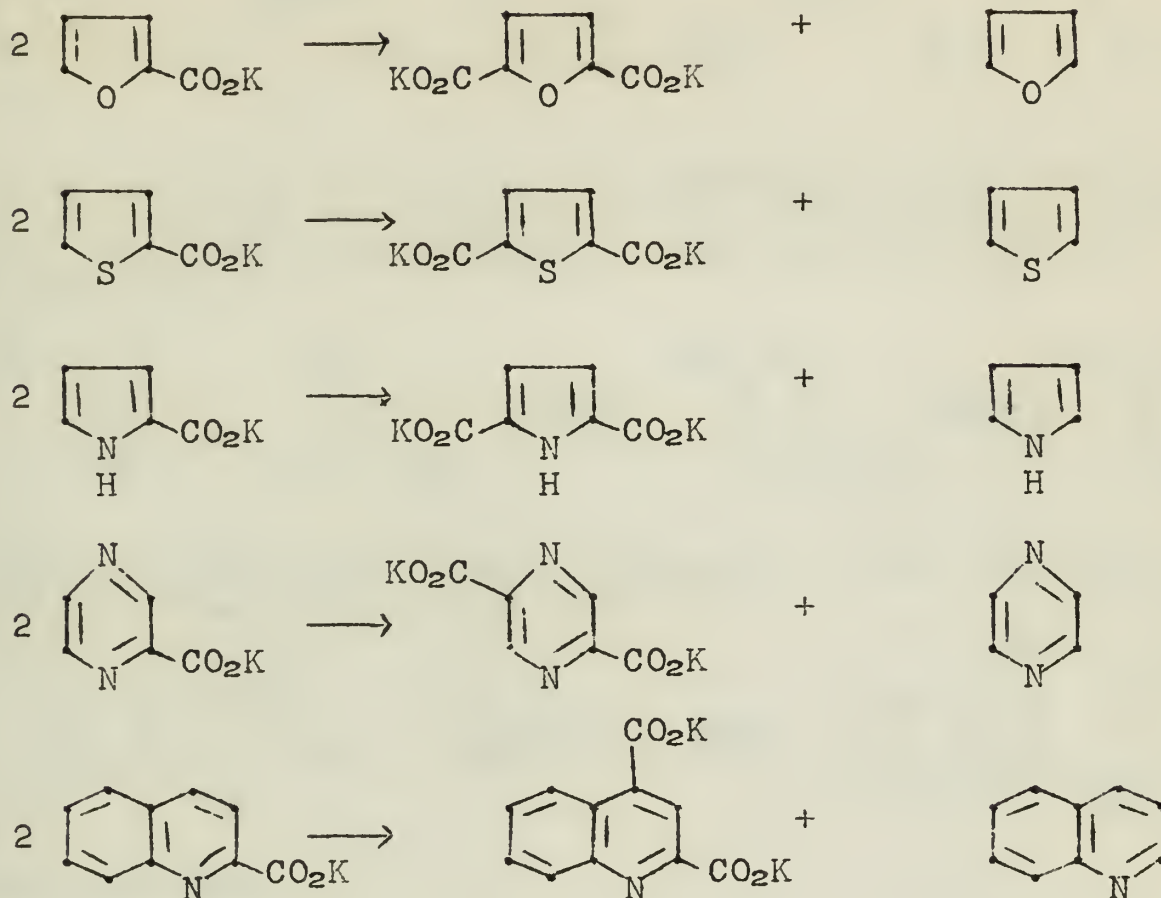
Mono-, di-, and tripotassium pyridinecarboxylate yield dipotassium 2,5-pyridinecarboxylate as the only product which can be isolated:



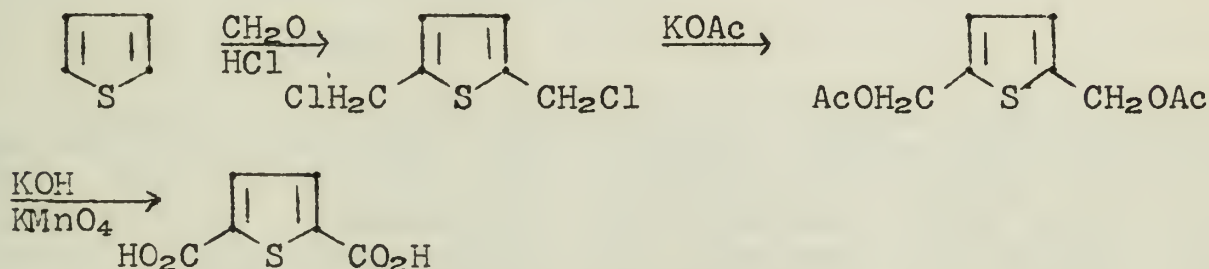




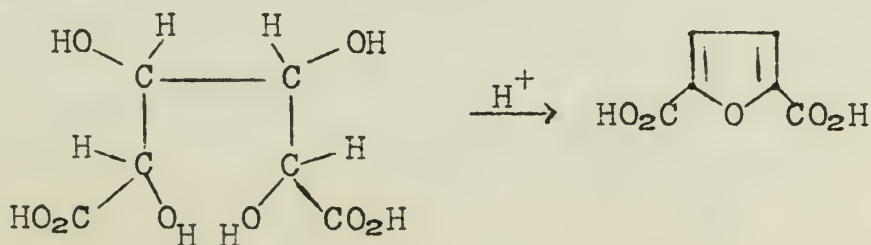
Several examples in which disproportionation appears to take place are also known:



Several of these heterocyclic aromatic acids are very hard to synthesize. This rearrangement may therefore provide a new, useful synthetic route. Thiophene-2,5-dicarboxylic acid was synthesized previously in fair yield by the following route (9):



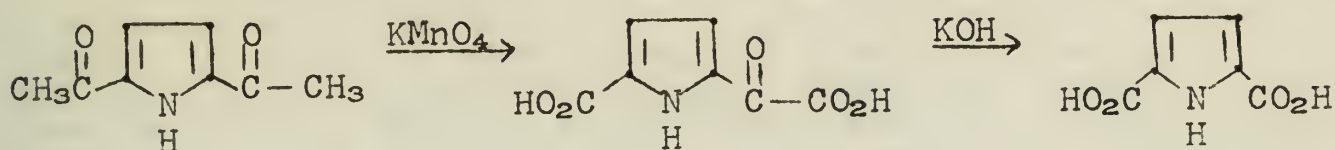
Furan-2,5-dicarboxylic acid is conveniently prepared from mucic acid:



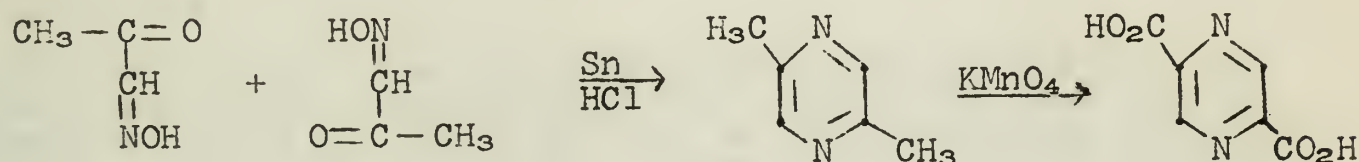




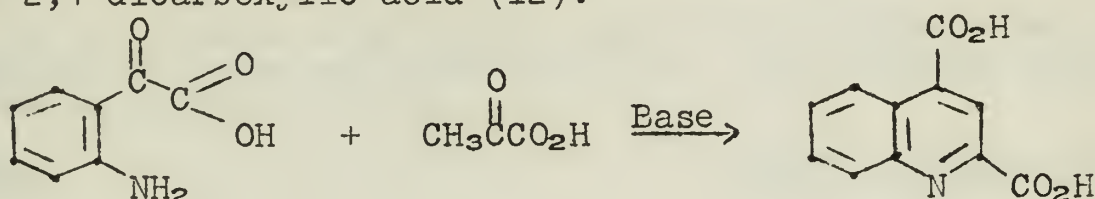
Pyrrole-2,5-dicarboxylic acid has been synthesized from the corresponding diacetyl compound (10):



The preparation of pyridine-2,5-dicarboxylic acid has been accomplished through the oxidation of the corresponding dimethylpyridine. Pyrazine-2,5-dicarboxylic acid has been similarly synthesized (11):



The Pfitzinger method has been employed in the synthesis of quinoline-2,4-dicarboxylic acid (12):



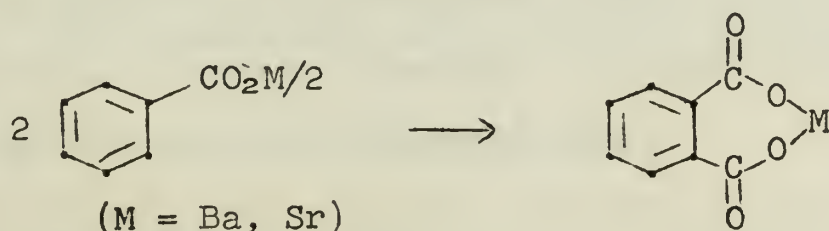
## REACTION CONDITIONS

### Temperature.

The reaction is most conveniently carried out at temperatures between 400 and 420°. It is quite slow at 350°, and above 450° a fair amount of decomposition takes place. Raecke claims that the reaction is slightly exothermic.

### Choice of Cation.

Potassium has proved to be the most useful cation. Rearrangement fails to take place with lithium. Sodium can be employed as a cation, but the reaction then requires more drastic conditions, which result in much decomposition. Rubidium and cesium work very well, however. Interesting results were obtained with the alkaline earth metals. Barium and strontium benzoate, on heating, afforded only the corresponding orthophthalic acid salt in good yield, while calcium benzoate yielded a small amount of a mixture of the possible three isomeric calcium phthalates.





### Pressure.

When Raecke initially investigated the reaction he found that a carbon dioxide pressure of ten to twenty atmospheres improved the yield. Therefore at first it was believed that the carbon dioxide gas might take part in the reaction. Meanwhile, suitable catalysts have been found, however, which render the use of carbon dioxide unnecessary. It appears that it largely serves as a protective gas to produce an inert atmosphere. Nitrogen, the rare gases and methane have also been used for this purpose. When cadmium iodide is used as a catalyst, even a pressure of 200 atmospheres of carbon dioxide will not affect the yield.

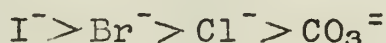
### Catalysts.

Virtually all of the more readily available metals have been tested as catalysts. Raecke found that cadmium and zinc are the two most effective catalysts; the use of cadmium affords yields of over 90%. Commonly the catalyst is added in the form of its halide salt, but according to Raecke cadmium vapor can also be blown into the reaction mixture with equal success.

A list of various metal cations and their effectiveness has been compiled by Ogata and coworkers (13). His findings agree with Raecke's observations:

<u>Metal</u>	<u>Yield of Terephthalate</u>
Cd	90%
Zn	50%
Ba, Sr, Ca, Mg	25%
Mn, Cu, Fe, Al, Pb, Hg, Ce, Zr, Th	15%
Sn, Co, Ti, La, Bi, Va, Na, K, Li	no catalytic effects
Ni	facilitates decomposition

Ogata also observed that the anion appears to play an important role, whereby he established the following relationship:



The oxides and sulfates of cadmium are also useful. Potassium iodide and iodine proved to be ineffective, however. Raecke also found cadmium and zinc phthalate to be good catalysts. It was noted that the catalysts derived from cadmium and zinc salts are reduced to metals to a considerable extent during the course of the reaction. This observation led to the introduction of zinc and cadmium metal, which also catalyzed the reaction very well.

### The Mechanism of the Rearrangement.

While Raecke has only been concerned with the synthetic aspects of the reaction, Ogata (13) has undertaken an attempt to elucidate the mechanism. Although he has not been very successful

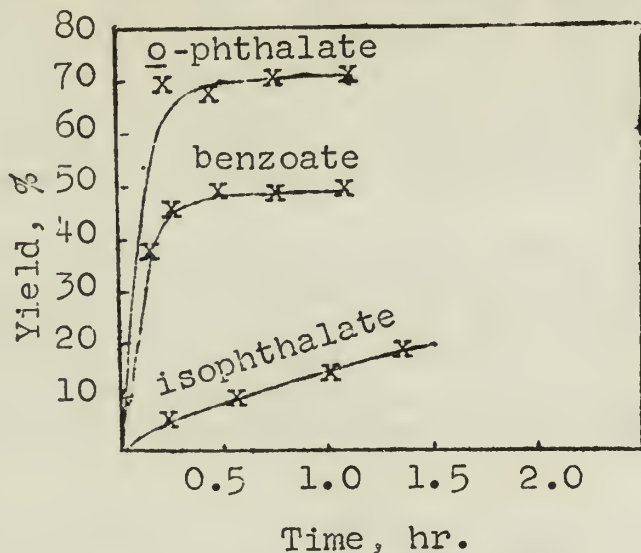




in advancing a suitable mechanism, his work nevertheless has been quite informative about a possible reaction path.

### Over-all Rate.

The over-all rate of the reaction was measured by Ogata by determining the yield of terephthalic acid as a function of time.



Cadmium iodide was used as a catalyst. When the reaction of the benzoate was run at 200 atmospheres pressure with carbon dioxide, no substantial increase in yield was observed.

### Tracer Work.

By the use of labeled cadmium carbonate,  $\text{CdC}^{14}\text{O}_3$ , as a catalyst, Ogata hoped to find out more about the mechanism of the rearrangement. He obtained the following data:

<u>Starting material</u>	<u>g. of catalyst</u>	<u>Temp., °C.</u>	<u>Time, hr.</u>	<u>Counts per min.</u>	<u>Substance counted</u>
$\text{p-C}_6\text{H}_4(\text{CO}_2\text{K})_2$	0.3	450	4	0	$\text{p-C}_6\text{H}_4(\text{CO}_2\text{K})_2$
$\text{o-C}_6\text{H}_4(\text{CO}_2\text{K})_2$	0.3	450	3	1105	
$\text{o-C}_6\text{H}_4(\text{CO}_2\text{K})_2$	0.2	450	3	485	
$\text{o-C}_6\text{H}_4(\text{CO}_2\text{K})_2$	0.1	450	3	312	
$\text{o-C}_6\text{H}_4(\text{CO}_2\text{K})_2$	0.2	410	3	677	
$\text{o-C}_6\text{H}_4(\text{CO}_2\text{K})_2$	0.2	390	1	646	
$\text{o-C}_6\text{H}_4(\text{CO}_2\text{K})_2$	0.2	390	1	56	$\text{o-C}_6\text{H}_4(\text{CO}_2\text{K})_2$
$\text{C}_6\text{H}_5\text{CO}_2\text{K}$	0.3	450	4	2	$\text{p-C}_6\text{H}_4(\text{CO}_2\text{K})_2$
$\text{C}_6\text{H}_5\text{CO}_2\text{K}$	0.2	470	2.5	192	$\text{p-C}_6\text{H}_4(\text{CO}_2\text{K})_2$
$\text{C}_6\text{H}_5\text{CO}_2\text{K}$	0.2	410	1	10	$\text{C}_6\text{H}_5\text{CO}_2\text{K}$

Several significant facts are shown in this table. The amount of radioactivity observed never exceeds one fifth of a mole of carbonylate. The amount of radioactivity in the product is a function of the amount of catalyst used. Terephthalate does not exchange under the reaction conditions, while recovered orthophthalate shows some radioactivity. Terephthalate derived from benzoate shows little radioactivity.

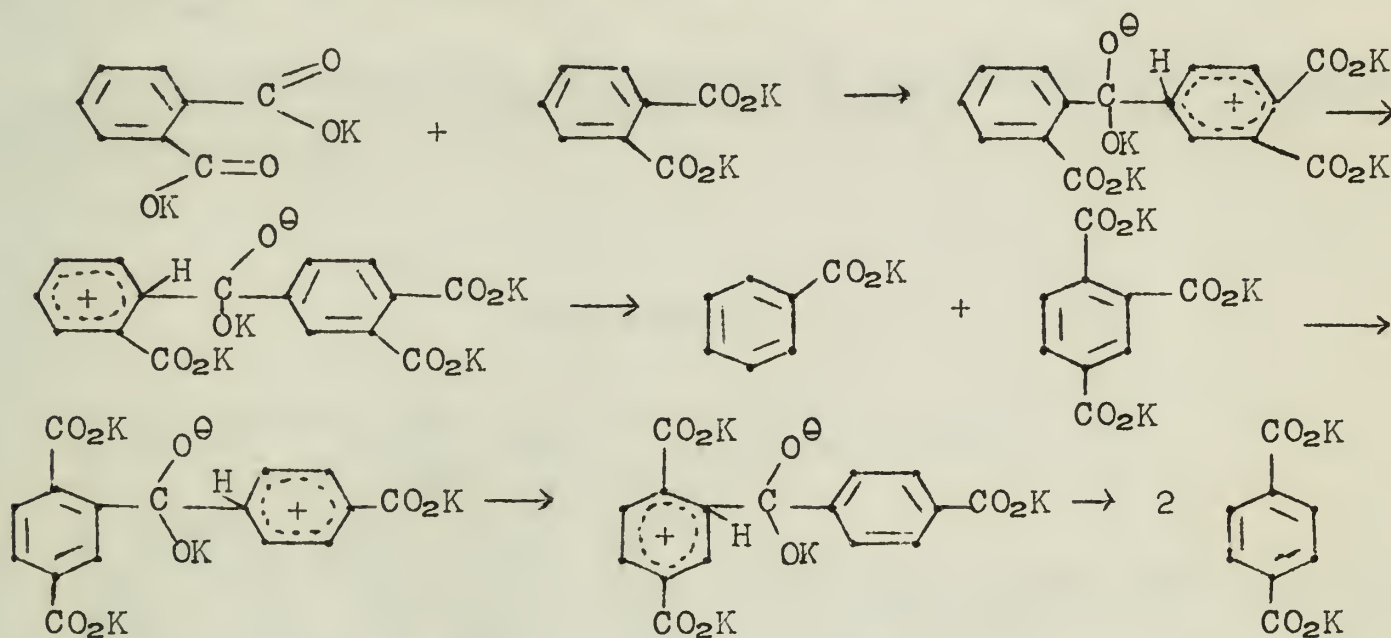
On the basis of his rate data and his tracer work Ogata therefore arrived at the following conclusions: (a) It appears to be





very unlikely that the initial step of the reaction is a decarboxylation followed by a recarboxylation, since even a pressure of 200 atmospheres of carbon dioxide showed no substantial increase in yield in the reaction of the benzoate; furthermore, the yield of terephthalate obtained from benzoate never exceeds 50%, if one assumes that one mole of the benzoate produces one mole of the terephthalate. (b) The isophthalate does not appear to be an intermediate in the rearrangement of the orthophthalate, since its rate of reaction is much slower. (c) Ogata also ruled out the benzoate as an intermediate in the rearrangement of the orthophthalate, since he felt that the rate of reaction of the benzoate was slower than that of the orthophthalate.

If one corrects for the fact, however, that orthophthalate will produce twice as much terephthalate as the benzoate does, it becomes apparent that the rate of the benzoate reaction is faster than that of the orthophthalate reaction. Benzoate therefore cannot be ruled out as an intermediate. A plausible mechanism which takes all the observed facts into account can be advanced as follows:



The first step is an attack of the benzene nucleus of orthophthalate, whereby it acts as a nucleophile, on the electrophilic carbon of a carboxylate group of another orthophthalate molecule. This is presumably followed by a 1,3 proton shift after which bond-breaking occurs to yield a tricarboxylate and benzoate. The benzoate then reacts with the tricarboxylate by a similar mechanism to afford the observed product.

At times 1,3,5-benzenetricarboxylic acid has been observed as a by-product in small yield. Raecke also claims to have observed some 1,2,4-benzenetricarboxylic acid. The formation of these compounds in the phthalate rearrangement makes the above mechanism attractive.

At the temperatures of the reaction the orthophthalate is molten, while the product, the terephthalate, at this temperature, starts to solidify as soon as it is formed. It is therefore possible that one is dealing with a series of equilibria from which the one



product which most readily solidifies is continuously being removed. Such a theory would explain the formation of the observed products in the analogous cases, since invariably the highest melting dicarboxylate is formed.

The role of the catalyst can also be explained on this basis. The transition state is stabilized by a cation capable of forming a covalent bond; cadmium and zinc probably are the most soluble and least volatile compounds. The fact that cadmium iodide catalyzes better than the corresponding bromide may be due to a better solubility, in view of the fact that potassium iodide and iodine have proved to be ineffective.

The observation of radioactive terephthalate from orthophthalate and labeled cadmium carbonate should probably be viewed as a separate reaction. A displacement reaction of radioactive carbonate on orthophthalate is possibly taking place. Such a reaction may be aided by steric acceleration, since radioactive terephthalate from benzoate has only been observed at higher temperatures.

An attempted reaction of potassium *p*-iodobenzoate and potassium *p*-bromobenzoate with cadmium carbonate failed to yield the desired terephthalate (13).

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# CYCLOBUTADIENE CHEMISTRY

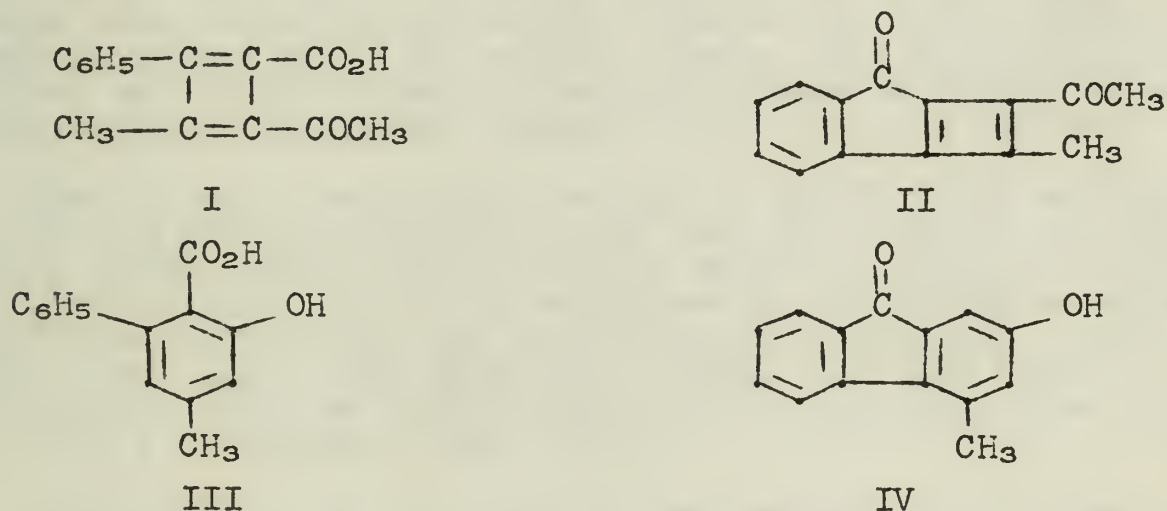
Reported by R. L. Harris

November 24, 1958

The synthesis of cyclobutadiene and its derivatives has been the object of speculation and experimentation for a number of years. This seminar will present the experimental efforts directed toward synthesis of cyclobutadiene derivatives and some of the conclusions arrived at by a mathematical treatment of cyclobutadiene according to various molecular orbital and valence bond methods.

One of the main reasons for the various attempts at synthesis of cyclobutadiene and its derivatives has been to ascertain whether these compounds are able to exist. None of the attempts at synthesis of cyclobutadiene and its simple derivatives seem to have been successful. Reports of the synthesis of a cyclobutadiene derivative have been shown in almost all instances to be in error. The failure to synthesize compounds of this type has led some experimenters to the conclusion that the compounds cannot exist and has stimulated others to further experimentation.

One of the first attempts at synthesis of cyclobutadiene was reported in 1905 by Willstätter and von Schmaedel (1). These workers were not able to isolate the compound. In the same year it was reported that compounds possessing structures I and II had been synthesized (2). This claim was later shown to be incorrect and the compounds isolated proved to have structures III and IV (3).



1,3-Diphenylcyclobutadiene was reported in 1914 to be formed by the action of sodium ethoxide on acetophenone (4). Although no further work has been done, this report seems open to question. A more recent report indicates that dimers of 1,3-diphenylcyclobutadiene are formed when the quaternary ammonium salt of 1,3-diamino-2,4-diphenylcyclobutane is treated with base (52). The synthesis of diphenylene was reported in 1911, but the properties of the material do not agree with those now accepted for this compound (5). One possible explanation of the instability of cyclobutadiene is that since it possesses only four  $\pi$  electrons, it does not conform to the  $[4n + 2]$  rule which attributes aromatic character only to those cyclic polyene systems possessing the number of electrons expressed





by the rule when  $n = 0, 1, 2$ , etc. (6). The simple molecular orbital theory leads to the prediction that the  $\pi$  electrons of cyclobutadiene are localized in the two double bonds, and that no resonance stabilization is possible (7,8). A further conclusion is that the ground state is degenerate, the triplet component becoming that of lowest energy in the next higher approximation (7,9). Consequently, cyclobutadiene would possess a diradical structure.

These results are in opposition to those obtained by valence bond methods of treatment of cyclobutadiene, which indicate that the molecule has a resonance energy ( $\alpha$ ) of about -1.5 e.v. (34 kcal.) (8,10). Thus, the molecule should possess aromatic properties and probably be stable. An attempt to reconcile the divergent conclusions has led to many modifications of the theories and also to newly developed ones.

One point generally agreed on is that the question of stability rests on electronic considerations rather than on steric influences. The earlier conclusion that the molecule did possess resonance energy had led to the belief that the instability must be due to steric strain in the molecule (10). By comparison with cyclobutene and cyclopropene, which do exist and should have similar ring strain, it is concluded that strain is not the most important factor in cyclobutadiene (6). Also, calculations have shown the strain energy of cyclobutadiene to be of the same magnitude as that of vinylacetylene, a stable compound (11). The reason for the divergence of the conclusions based on the two general methods seems to be that the molecular orbital theory neglects electronic interaction while the valence bond method puts too much emphasis on this interaction or resonance splitting of the energy levels. The results of a number of modified molecular orbital calculations tend to attribute some delocalization (resonance) energy to the molecule (12-16).

The "atoms in molecules" method of Moffitt (17) was also applied and agrees fairly well with the Anti-Symmetrical Molecular Orbital (ASMO) method used by Craig, which includes all electron repulsion integrals (9). By reference to calculated energies of structures varying from the square to the rectangular, having normal double and single bond distances, Shida concluded that the square structure will not be stable and that, if cyclobutadiene exists, it will take a rectangular form (14).

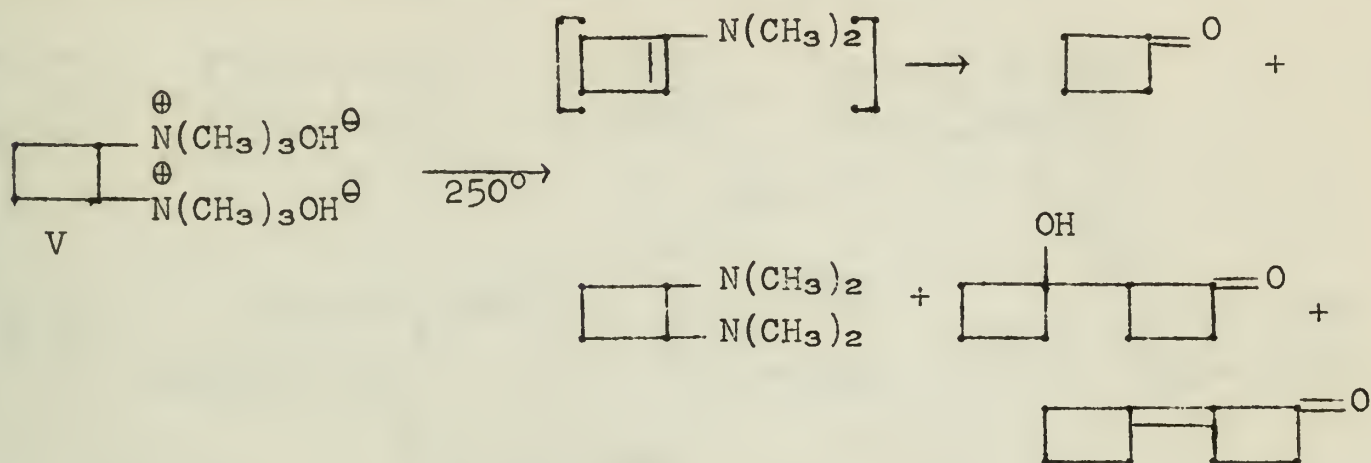
Modifications of the valence bond method lead to the conclusion that the resonance energy is not as high as that predicted by the simple valence bond theory (18,19). The modified valence bond method of McWeeny (20), involving all possible nonpolar, polar, singlet, triplet, doubly polar, etc., states of the molecule produces a result that is in fairly good agreement with Craig's ASMO method (9). Since agreement on the structure of cyclobutadiene has not been reached, the ability of the molecule to exist is still in question. Toward the clarification of this problem, various recent attempts at synthesis of cyclobutadiene derivatives have been reported.

The synthesis of cyclobutadiene itself was attempted again in 1942 by E. R. Buchmann and coworkers by a Hofmann reaction on the di-quaternary ammonium hydroxide V. (21). A number of products were isolated, but no cyclobutadiene was produced. It was later thought possible that 1,3-diaminocyclobutane would be a better candidate for

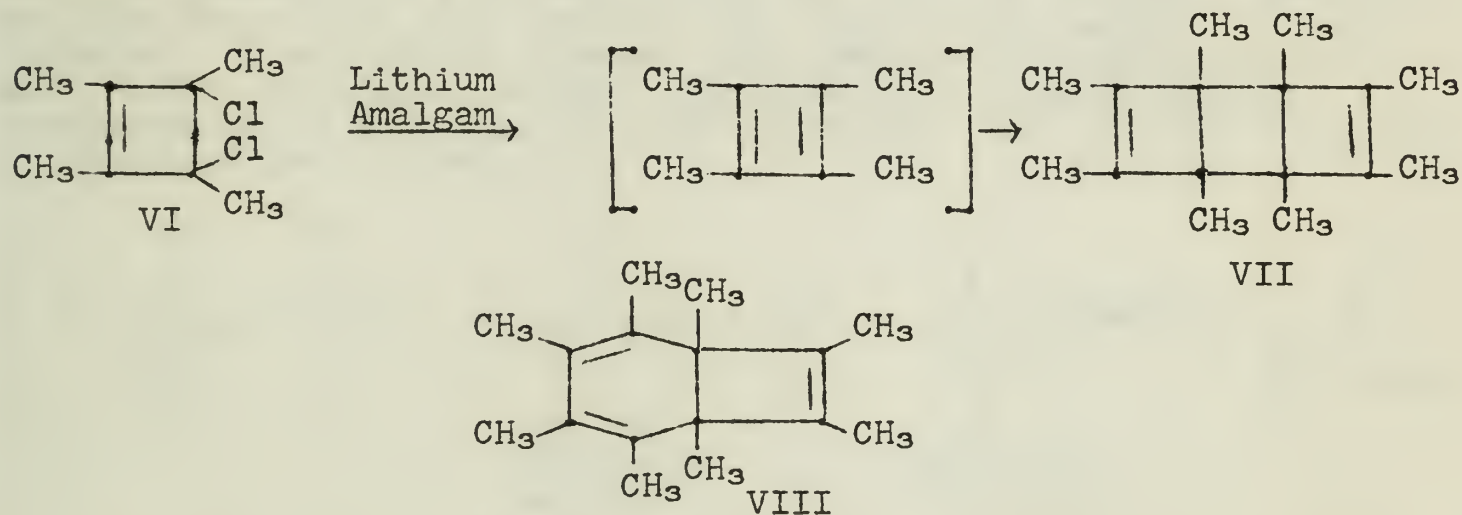




the Hofmann methylation procedure, but once again no cyclobutadiene could be isolated (6). In this reaction, a 20 percent yield of butadiene was realized. The butadiene could have arisen from cyclobutadiene by abstraction of two hydrogen atoms from another component of the reaction mixture.



Another recent example of attempted synthesis of a simple derivative is that of tetramethylcyclobutadiene (22). In this reaction, it is likely that the compound was actually produced and became stabilized by dimerization. The reaction was carried out by the action of lithium amalgam on 3,4-dichloro-1,2,3,4-tetramethyl-1-cyclobutene (VI). The compound isolated is reported to have structure VII.



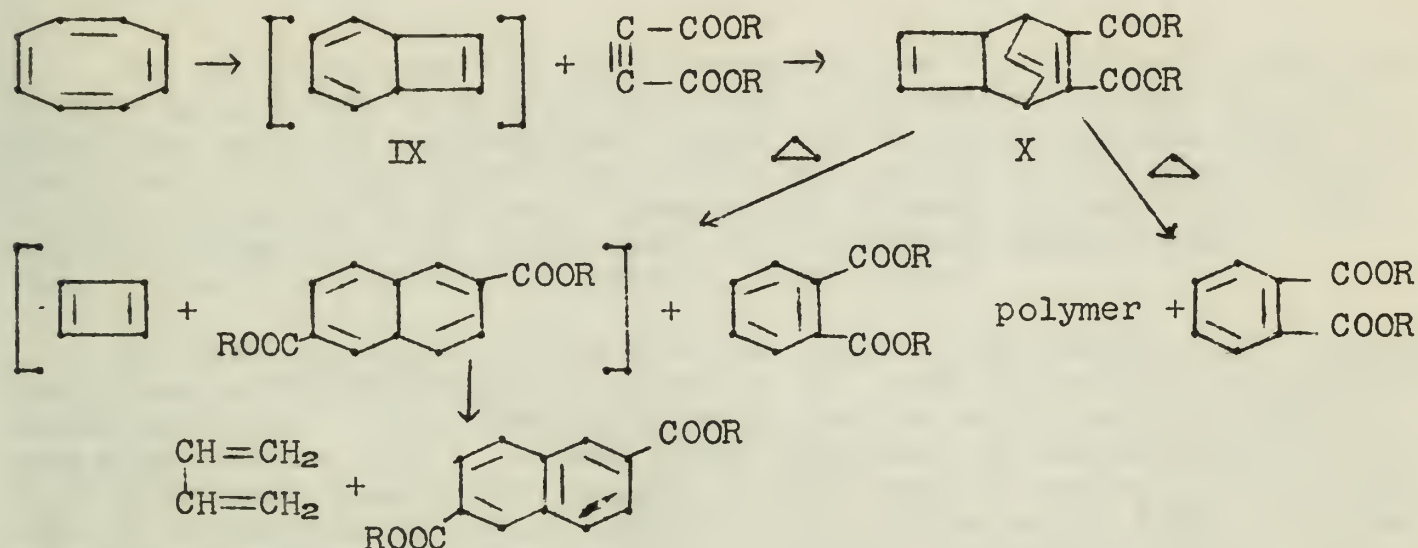
The only question which might be raised is that of the structure of the dimer, since it has been reported that the action of zinc on the same starting material VI produces a cyclobutadiene dimer assigned structure VIII (23). This structure could be formed by an electron shift in VII and might be favored on the basis of producing a six-membered ring with conjugated double bonds rather than two fused four-membered rings. This type of rearrangement has been shown to take place in the case of the benzocyclobutadiene dimer, to be discussed later (24).

Another reaction which might be expected to produce cyclobutadiene is the thermal decomposition of the Diels-Alder adducts of cyclooctatetraene and such compounds as 1,4-naphthoquinone and esters

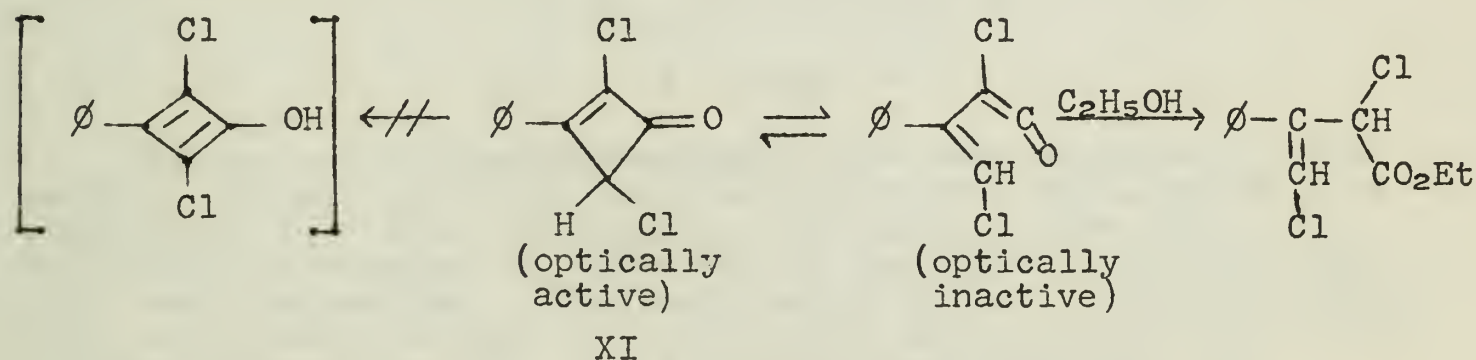




of acetylene dicarboxylic acid. The tetraene reacts as if it possessed structure IX. When an adduct such as X was heated, phthalic acid esters could be isolated, but the other product was a resinous polymer (25). When the same reaction was carried out by Nenitzescu, butadiene and an ester of 2,6-naphthlenedicarboxylic acid were isolated in addition to phthalic acid ester (6).

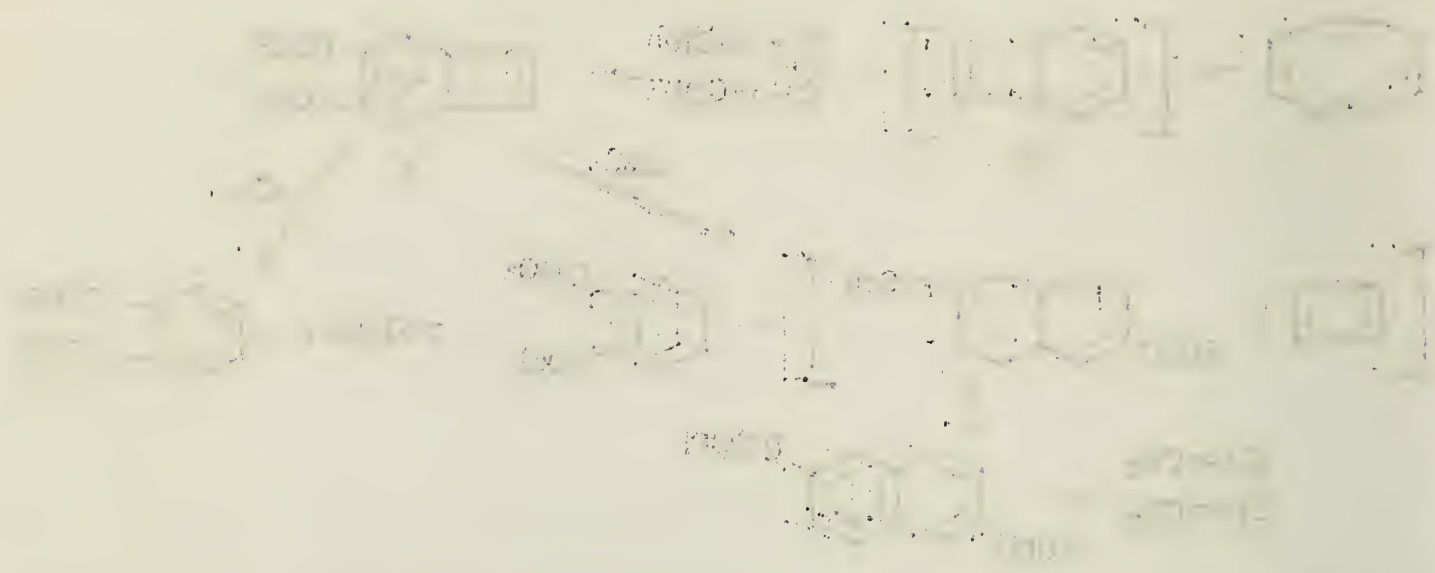


The possibility of the existence of a cyclobutadiene ring system has also been entertained in the racemization of compound XI (26,27). Although the ketone XI gives no color with ferric chloride, does not show the presence of a hydroxyl group by infrared analysis, and does not form an acetate when treated with isopropenyl acetate, it does racemize. It was shown, however, that when an optically active form was treated with  $\text{D}_2\text{SO}_4$  or  $\text{DOAc}$ , racemization did occur without incorporation of deuterium into the molecule. The proposed mechanism of racemization is shown:

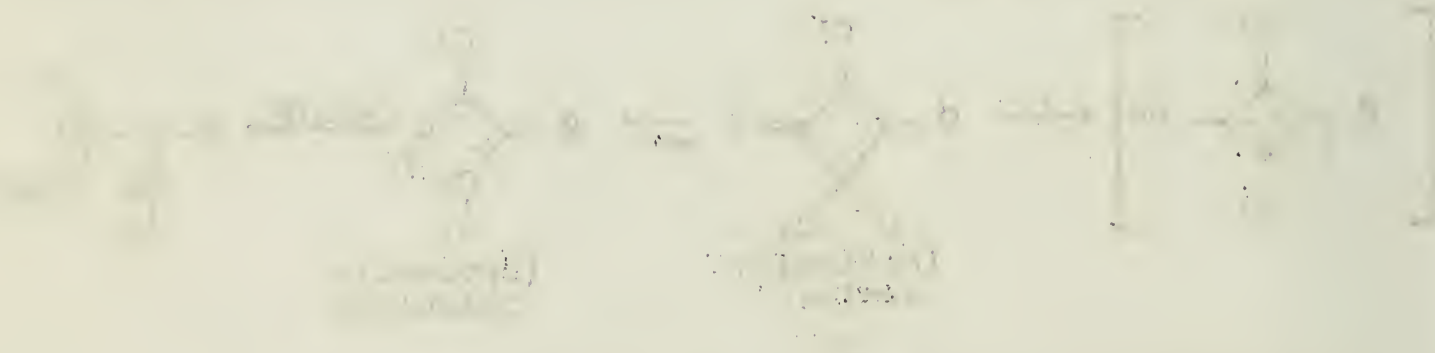


An interesting example of a compound which, although not possessing two double bonds in the ring, bears a relationship to cyclobutadiene is XII, called phenylcyclobutadienoquinone (28). It has not been found possible to hydrogenate XII to a hydroquinone, which would be a true cyclobutadiene compound; zinc with hydrochloric acid converts the compound to phenylcyclobutane. No reactions have been found which place two double bonds in the ring, but some of the substitution products are of interest. For example, the hydroxy derivative XIII is believed to be one of the strongest acids of any compound containing only carbon, hydrogen, and oxygen. It has a  $\text{pK}_a$  of about 1.0 (29).

The following is a list of the names of the persons who have been appointed to the various committees of the Board of Directors of the City of New York, for the year 1901. The names are given in alphabetical order, and the committees to which they are appointed are indicated by the numbers in parentheses.

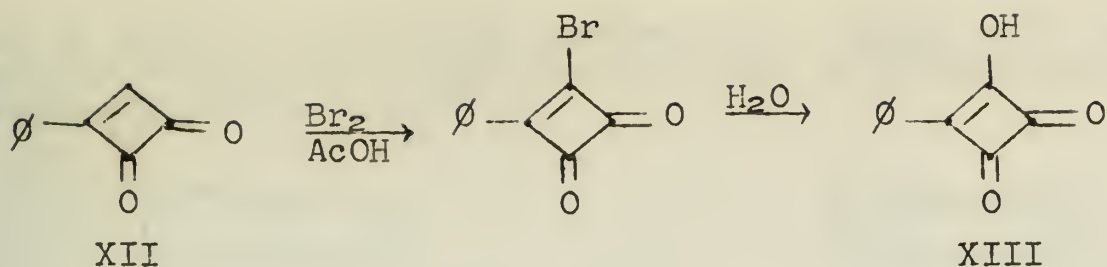


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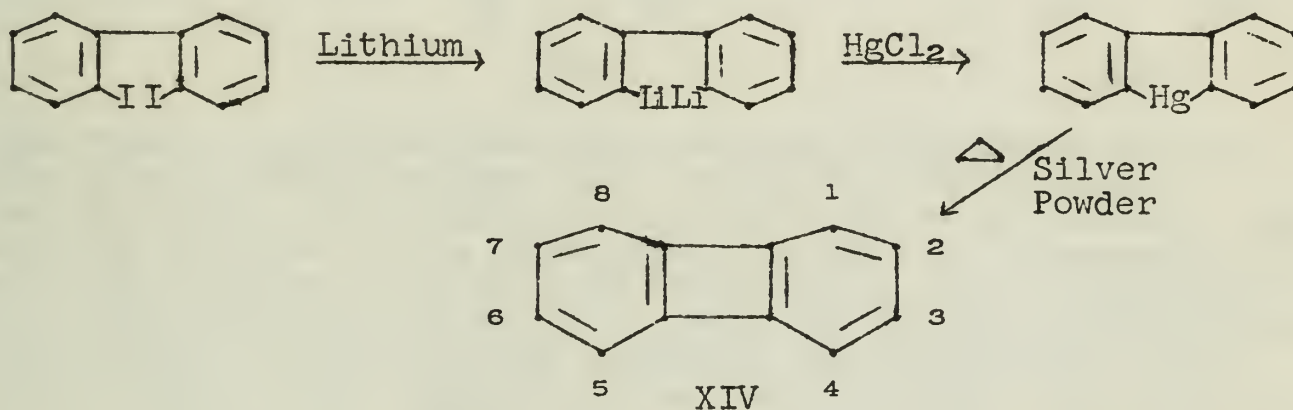
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The existence of XII also lends support to the theory that ring strain is not the most important factor in the stability of cyclobutadiene and its derivatives, since, to a first approximation, it is expected to have about the same ring strain as phenylcyclobutadiene. It is of additional interest that heat of combustion data indicate that XII has 30-40 kcal. of resonance energy after correction for that of the benzene ring (30).

It has been only in the area of fused ring systems that compounds have been synthesized which possess, at least formally, a cyclobutadiene nucleus. The first fused ring derivative of cyclobutadiene was diphenylene, XIV. It was first produced by the distillation of 2,2'-dibromobiphenyl with cuprous oxide, and in better yield by the use of biphenyleneiodonium iodide with cuprous oxide (31). It has also been produced by the reaction sequence indicated below (32).



Various substituted diphenylenes have been prepared by these methods, in addition to heating the tetrazonium salts formed from substituted 2,2'-diaminobiphenyls with cuprous oxide (33). The following are examples of compounds of the diphenylene type which have been synthesized: 1,2-dinaphthalene (34), 2,3-dinaphthalene (33), benzo(a)diphenylene (34), 2,7-dimethyldiphenylene (31), 1,8-dimethyldiphenylene (35), and 2,7-dimethoxydiphenylene (35).

It might be mentioned at this point that there is a question as to the position of the double bonds in the rings of diphenylene. One viewpoint would be that diphenylene consists of two separate benzene type systems, bearing only a formal analogy to cyclobutadiene. Another view might be that all three rings are part of a resonance hybrid system, and that a structure such as XV might contribute to the resonance hybrid. Another viewpoint that is held by some investigators is that the double bonds would be localized in the positions shown by XVI, so that the four-membered ring may be in the less strained cyclobutane form. This supposition is based on work by Mills and Nixon on the position of double bonds when the benzene



ring is fused to other ring systems (36). Additional work has shown that the Mills-Nixon effect does operate in certain molecules, notably hydrindene (37,38).

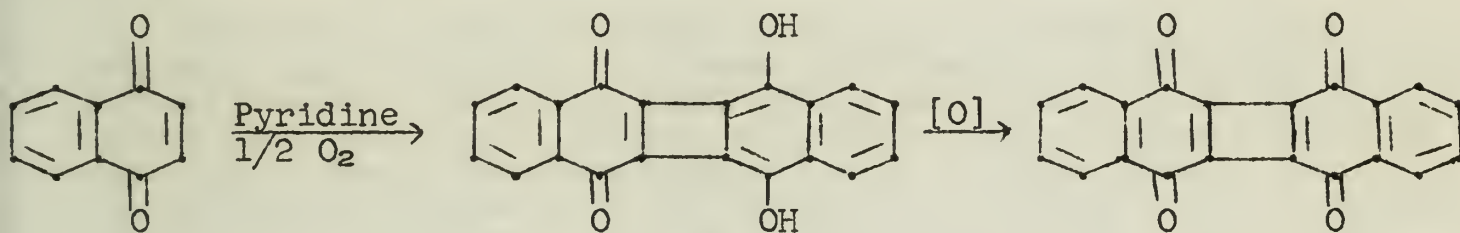


XV



XVI

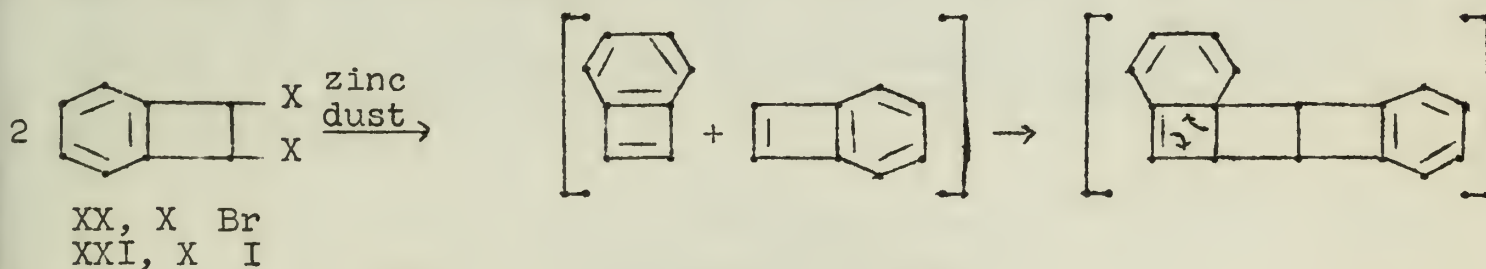
In another study, carried out in 1937, it was reported that heating 1,4-naphthoquinone with pyridine in the presence of air produced a quinhydrone XVII, which, when heated with nitrobenzene, yielded the quinone XVIII (39). The distillation of XVIII with zinc dust was reported to yield 2,3-dinaphthalene. Further work by Bell and Hunter has shown that a quinone of the reported properties was easily obtained, but that no hydrocarbon could be realized by zinc dust distillation (50).



XVII

XVIII

The fused ring system that has been most intensively studied recently is benzocyclobutadiene (19), named cyclobutabenzene in Chemical Abstracts. The compound has been found to be unstable, and its dimer is isolated in the experiments in which it is assumed to be formed. The compound XX is made by treating  $\alpha,\alpha,\alpha',\alpha'$ -tetrabromo-*o*-xylene with potassium iodide (24). This dibromide, or the diiodide XXI, when treated with zinc dust, produces cyclobutadiene, which undergoes a Diels-Alder dimerization and rearrangement of bonds to produce the stable dimer XXII.



XXII

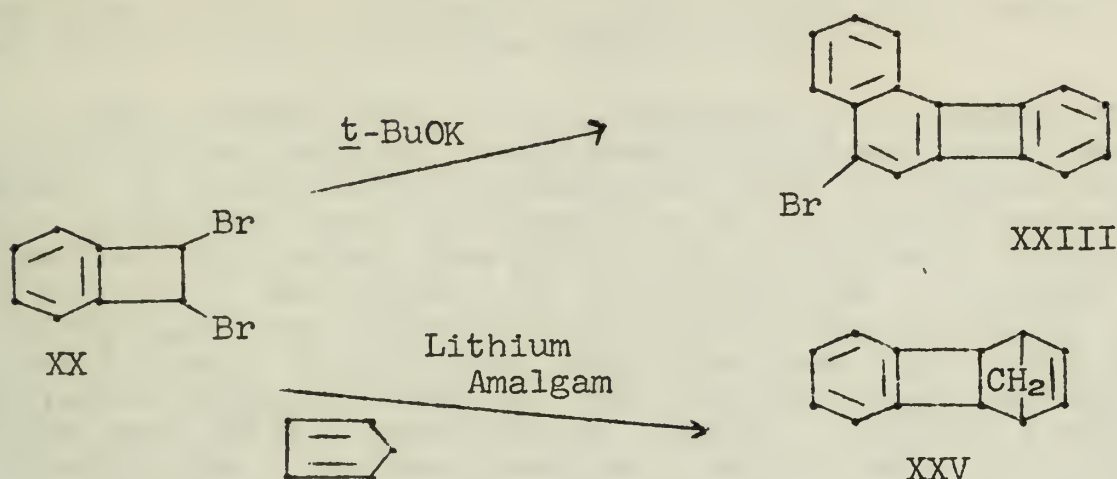
As is indicated, dehydrogenation with N-bromosuccinimide produces the known benzo(a)diphenylene.

When the dibromide XX is subjected to dehydrohalogenation conditions rather than dehalogenation, a similar type of reaction



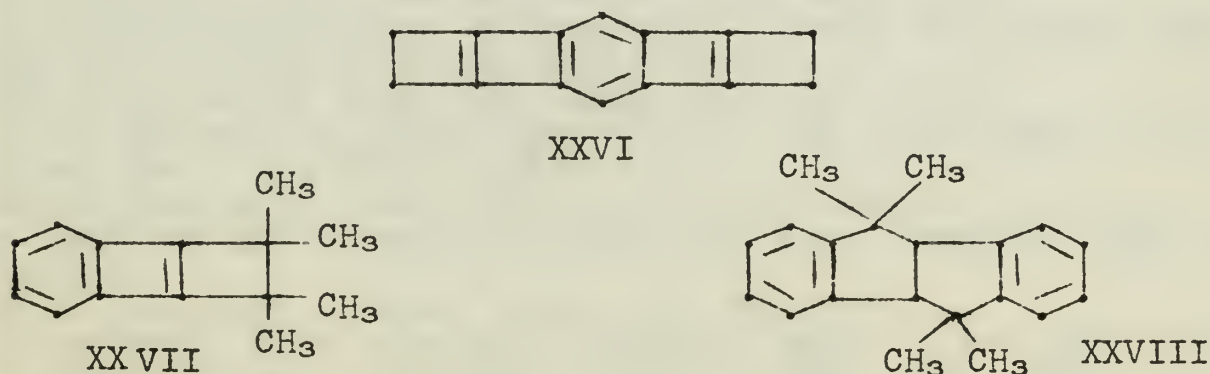


occurs to produce a dimer. Under the experimental conditions, the reaction proceeds further to produce the completely aromatic bromo dimer XXIII (40).



Treatment of the dimer XXIII with *n*-butyllithium, followed by methanol, again produced the known hydrocarbon 1,2-benzodiphenylene. The structure of the bromo dimer XXIII was proved by an independent synthesis, involving a general method for diphenylenes of heating the substituted 2,2'-diiodobiphenyl with cuprous oxide. The 5-bromobenzo(a)biphenylene was identical with that from the dehydrohalogenation reaction. Another reaction of similar type is the dehydrohalogenation of 1-bromobenzocyclobutene (41). The action of potassium *t*-butoxide produced the benzocyclobutadiene dimer XX. A modification of the above reactions has been shown to produce an interesting product. The dibromide XX was converted to XXV when heated with lithium amalgam in the presence of cyclopentadiene (51).

Two further examples of benzocyclobutadiene derivatives have been reported by Lagidze and coworkers. The first was formed by the reaction of the diacetate of 2-butyne-1,4-diol with benzene in the presence of aluminum chloride (42). The product was reported to have structure XXVI. This reaction attracted much attention since the product was so unusual. After further work on the reaction, Hancock and Taber (43), Maier (44), and Fenton and coworkers (45) all arrived at the conclusion that the hydrocarbon reported was in actuality 2-phenylnaphthalene. Other products reported have also been identified.



The reaction is believed to involve 2,3-diphenyl-1,3-butadiene as an intermediate, with a cyclization and rearrangement taking





place to produce the 2-phenylnaphthalene (43). The other example is of a similar type. It was reported that the reaction of the diacetate of 1,1,4,4-tetramethyl-2-butyne-1,4-diol with benzene and aluminum chloride yielded a product of structure XXVII (46). This has been shown to be identical with a compound prepared by Smith and Wright having structure XXVIII (47,48).

As a closing note, it is interesting to contemplate the possibilities outlined by Longuet-Higgins and Orgel regarding a method of stabilizing cyclobutadiene and its derivatives (49). They have postulated that the formation of a  $\pi$  electron complex of cyclobutadiene with metal ions will tend to produce a stable compound. In support of the theory, it was shown that a compound of formula  $\text{Ni}(\text{CN})_2(\text{C}_4\text{H}_4)$  may be an intermediate in the synthesis of cyclo-octatetraene. In addition, when acetylene was passed into a palladous chloride solution, the compound  $(\text{C}_4\text{H}_4)\text{PdCl}(\text{OH})$  was formed which when treated with alkali, yielded a product containing butyraldehyde. Another compound found to exist was that of formula  $\text{C}_7\text{H}_4\text{O}_3\text{Fe}$ . Since it reacted like an iron carbonyl compound, it is possible that it might be formulated as  $\text{Fe}(\text{CO})_3(\text{C}_4\text{H}_4)$ . It must be stated, however, that a carbon isotope study indicates that an intermediate of this type to be improbable during the reaction of acetylene and acrylonitrile (53). An X-ray study has also ruled out such a structure for  $\text{Fe}_2\text{C}_{10}\text{H}_8\text{O}_8$  (54).

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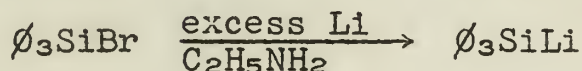
# TRISUBSTITUTED SILYL ALKALI METAL COMPOUNDS

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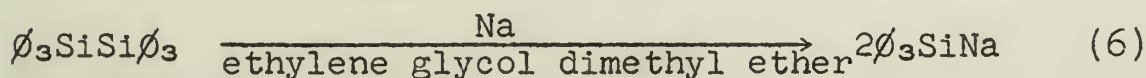
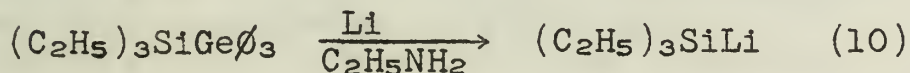
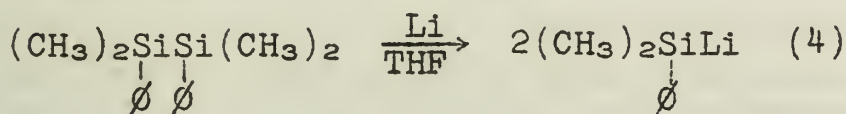
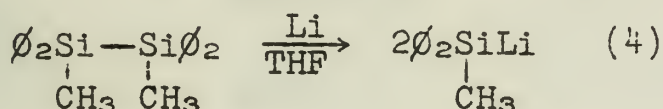
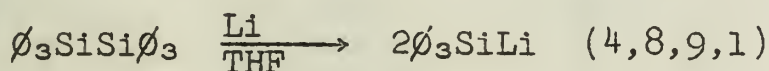
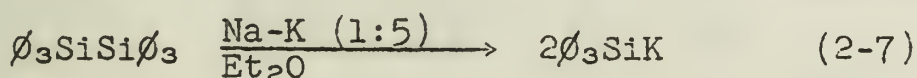
December 1, 1958

## PREPARATION

The first synthesis of an organosilane containing a silicon-alkali metal bond was reported in 1933; triphenylsilyllithium was prepared in low yield according to the following equation (1).



The synthesis of compounds of this type has been extended, mostly in recent work by Gilman. The following equations illustrate the preparations of all known silyl-alkali metal compounds. Where more than one reference is cited the first reference gives the method of best yield.



## REACTIONS

Many of the reactions of trisubstituted silyl alkali metal compounds are those which would be expected from experience with organo-metallic compounds: the trisubstituted silyl group behaves as a nucleophile, displacing a halogen atom, attacking a carbonyl carbon atom, or undergoing hydrolysis to give the trisubstituted silane.

These "normal" reactions of  $\text{R}_3\text{SiM}$  compounds are summed up in Table I. The yields given are the best reported. Reactions giving product in less than 30% yield have been omitted unless they illustrate a type of reaction not otherwise included in the table. However, all omitted reactions are available in the references cited.





Table I

Normal Reactions of Compounds of the Type  $R_3SiM$ 

Co-reactant	$\phi_3SiK$			$\phi_3SiLi$		
	Product	%	Ref	Product	%	Ref
$\phi I$	$\phi_3Si\phi$	63	12			
$\phi Br$	$\phi_3Si\phi$	61	14			
$\phi Cl$	$\phi_3Si\phi$	54	12			
$\phi F$	$\phi_3Si\phi$	12	12			
p- $CH_3C_6H_4Br$	p- $CH_3C_6H_4Si\phi_3$	95	12			
o- $CH_3C_6H_4Br$	o- $CH_3C_6H_4Si\phi_3$	57	12			
$\phi CH_2Cl$	$\phi_3SiCH_2\phi$	39	12			
$(CH_3)_3SiCl$	$\phi_3SiSi(CH_3)_3$	86	12	$\phi_3SiSi(CH_3)_3$	79	4 <sup>1,2</sup>
$(C_2H_5)_3SiCl$	$\phi_3SiSi(C_2H_5)_3$	27	16			
$\phi_2SiCl_2$	$\phi_3SiSi\phi_2Si\phi_3$	53	12 <sup>3</sup>			
$NH_4Br$				$\phi_3SiH$	-	1 <sup>4</sup>
$\phi_3SnCl$	$\phi_3SiSn\phi_3$	86	12			
$CO_2$	$\phi_3SiCO_2H$	80	15			
$CH_2O$	$\phi_3SiCH_2OH$	-	11			
$CH_3CHO$				$\phi_3SiCH(OH)(CH_3)$	39	18
$CH_3COCH_3$				$\phi_3SiC(OH)(CH_3)_2$	52	13 <sup>1,2</sup>
$H_2O$	$\phi_3SiH$	-	12			

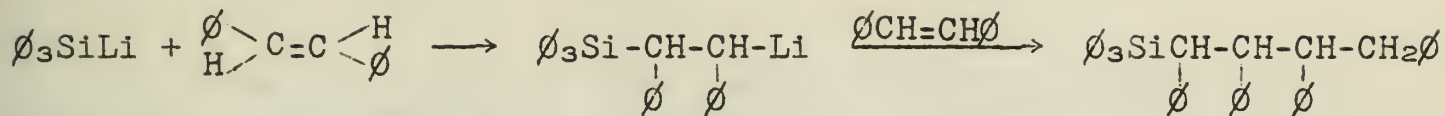
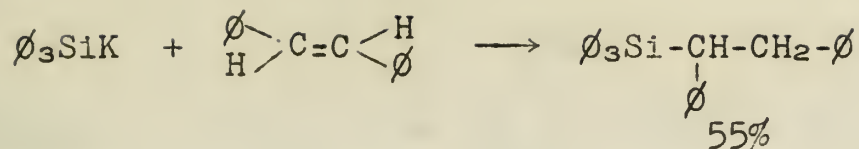
1. Similarly for  $\phi_2(CH_3)SiLi$ , same reference.
2. Similarly for  $(CH_3)_2(\phi)SiLi$ , same reference.
3. Two mole equivalents of  $\phi_3SiK$  used.
4. Similarly for  $(C_2H_5)_3SiLi$ , same reference.

The reactions indicated above and those which are discussed below always involve a hydrolysis prior to work up, in the same manner as the more familiar handling of organometallic compounds. Where this step is not indicated it should be assumed present.

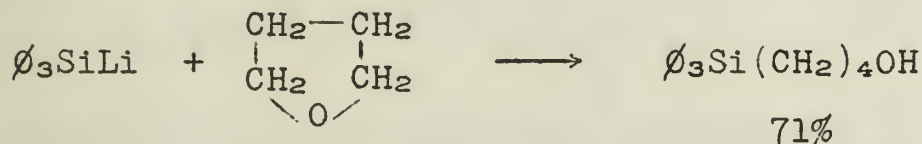
Of more immediate interest than these normal reactions of  $R_3SiM$  compounds are those reactions in which the products are of a nature not predicted by analogy with carbon chemistry. The influence of the silicon atom which leads to the formation of these abnormal products exerts itself either in the initial reaction of the silyl-alkali metal compound with its co-reactant or in the rearrangement or further reaction of an otherwise normally formed product.

As an example of the former type may be taken the ability of triphenylsilylpotassium (3) and triphenylsilyllithium (19) to add to the double bond of trans-stilbene. The inability of the silicon atom to form double bonds with a carbon atom (5,20-27) prohibits resonance stabilization of the triphenylsilyl anion and renders it more reactive than the triphenylmethyl anion, which does not undergo addition to this unsaturated system.

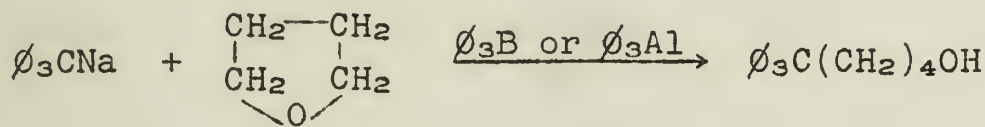




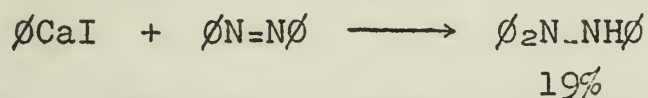
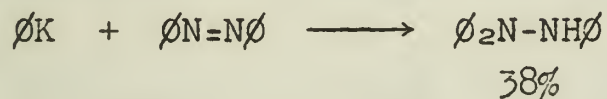
The ability of triphenylsilyllithium to open the ring of tetrahydrofuran under strenuous conditions is another example of the high reactivity of these compounds (17,28).



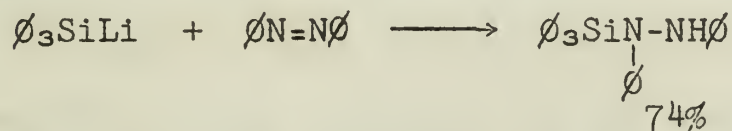
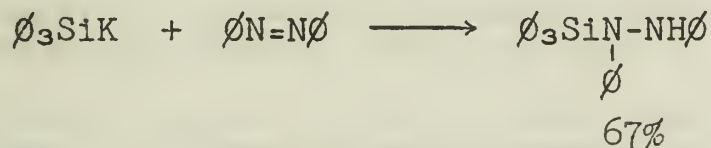
Triphenylmethylsodium attacks tetrahydrofuran only if a catalyst is present (29,30).



The only organometallic compounds known to add to the lateral double bond of azobenzene are the highly reactive phenylpotassium and phenylcalcium iodide (31).



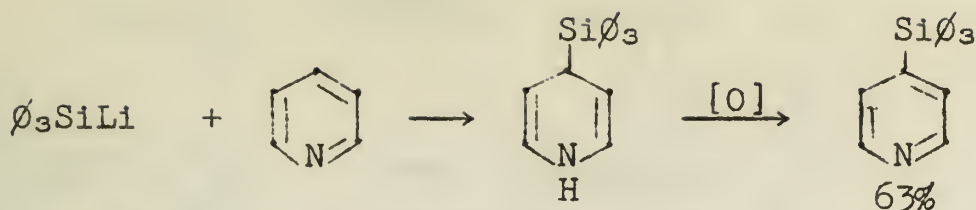
Triphenylsilylpotassium and triphenylsilyllithium react smoothly at room temperature (32).



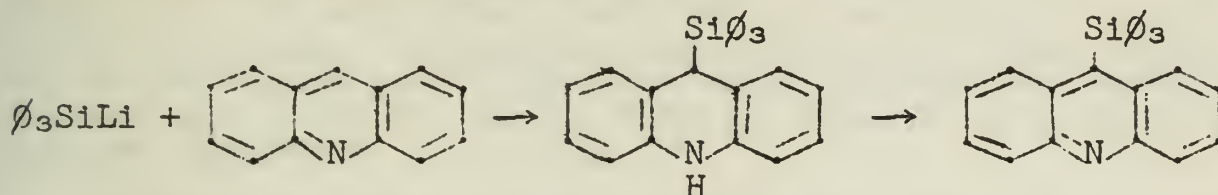
Triphenylsilyllithium exhibits a high degree of reactivity in its ability to react in good yield with pyridine. Curiously, the reaction is entirely at the 4-position, an observation which has not been explained. It has been shown, however, that benzylmagnesium chloride and allylmagnesium bromide give yields of 25% (33) and 9% (34), respectively, of the corresponding 4-substituted pyridines together with smaller amounts of the 2-isomers; organolithium reagents react in the 2-position (35).



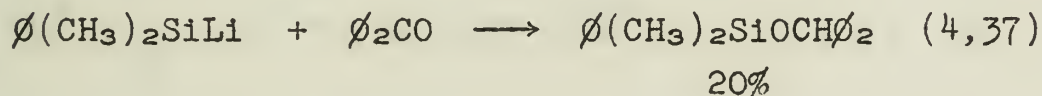
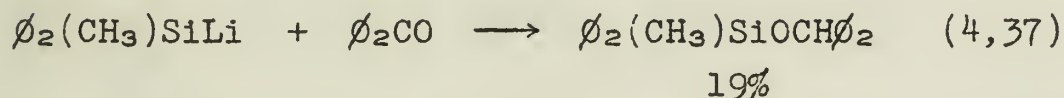
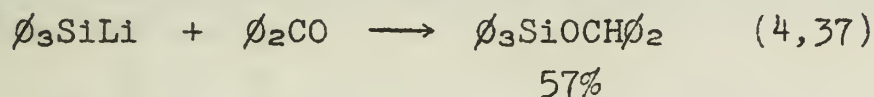
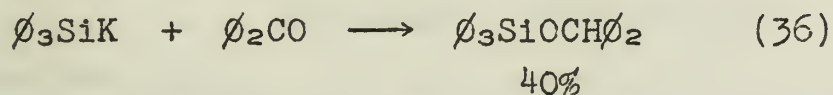




Acridine, as might be anticipated, suffers attack at the 9-position on treatment with organolithium reagents, and triphenylsilyllithium behaves similarly (46).

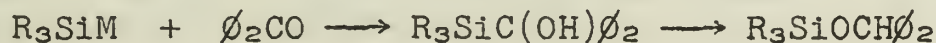


Reactions yielding abnormal products due to the instability of an otherwise normally formed compound are of fairly common occurrence. Most notable among these are the ethers resulting from the rearrangement of diaryltriphenylsilylcarbinols.



It is interesting to note that the inability of the triphenylsilyl group to exist as a resonance-stabilized free radical completely prohibits pinacol formation in the reactions indicated above. By comparison, the reaction of triphenylmethylmagnesium chloride with benzophenone yields benzopinacol in a 93% yield (38). Triphenylmethylsodium behaves similarly (39).

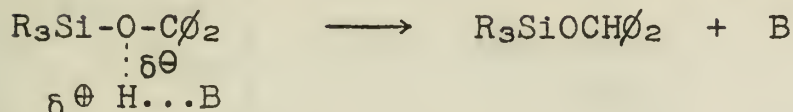
These ethers probably result from normal reaction to form the carbinol, followed by rearrangement to the ether (40).



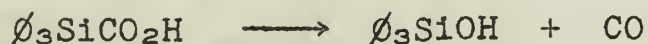
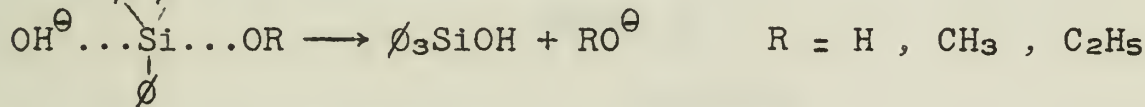
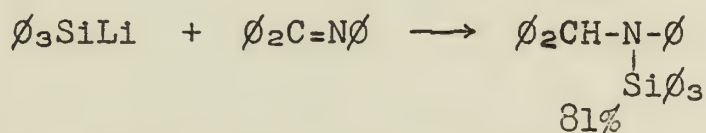
In support of this viewpoint it has been demonstrated that catalytic amounts of basic materials such as pyridine, sodium hydroxide, silver oxide, sodium, sodium-potassium alloy, and sodium hydride cause the rearrangement of these carbinols in very high yield, under relatively mild conditions (40). The mechanism is given as:





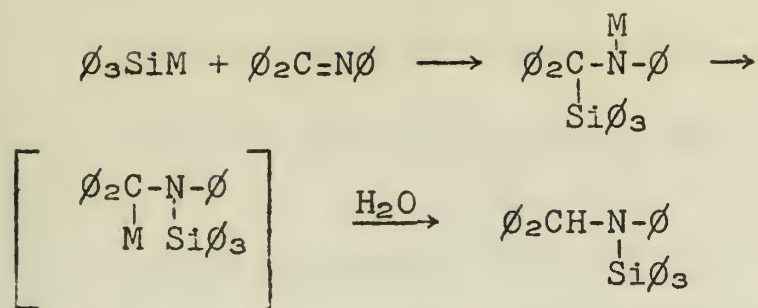


Triphenylsilanecarboxylic acid, resulting from the carbonation of triphenylsilylpotassium (see Table I) is stable only in the complete absence of base, and undergoes a unique decarbonylation if base is present (15).

[illegible]
$$\text{SiK} + \text{C}=\text{N} \longrightarrow \text{CH}-\text{N}-\underset{\text{SiK}}{\underset{81\%}{\text{C}}}$$


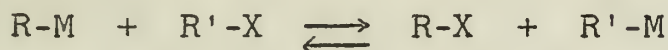
It has been suggested (32) that the product may result from normal addition followed by a rearrangement analogous to those of the silyldiphenylcarbinols already mentioned.





# HALOGEN-METAL INTERCONVERSIONS

Halogen-metal interconversions may be expressed in general as:



The equilibrium favors the attachment of the alkali metal to the more electronegative radical (45). A familiar example is the use of n-butyllithium to replace a halogen atom by the lithium atom. The study of this type of reaction in the silane series arose when it was pointed out that, although triphenylsilylpotassium is apparently a highly reactive compound, the yields of its coupling products with organic halides are often unexpectedly low. In an attempt to explain this fact a careful study was made of a number of such reactions. The reaction between triphenylsilylpotassium and bromobenzene may be taken as typical (14).



The yields for method A (addition of  $\phi\text{Br}$  to  $\phi_3\text{SiK}$ ) and method B (reverse addition) are shown in Table II.

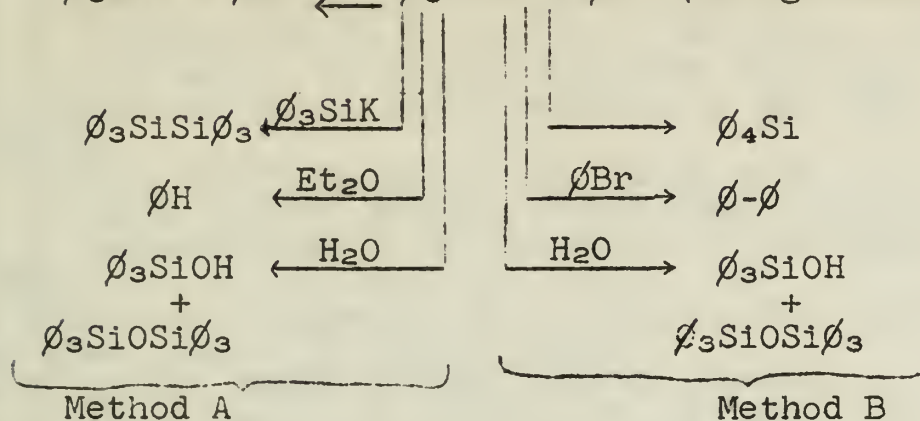
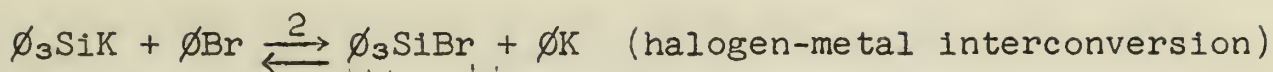
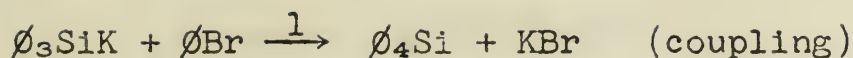
Table II

	Products	yields	
		A	B
I	$\phi_4\text{Si}$	55%	61%
II	$\phi_3\text{SiSi}\phi_3$	22	0
III	$\phi_3\text{SiOH}$	5	1
IV	$\phi_3\text{SiOSi}\phi_3$	4	34
V	$\phi\text{H}$	9	trace
VI	$\phi-\phi$	0	8

The following scheme, involving two routes (1 and 2) is suggested to explain these results.







The following explanations are given for the marked variations in yield cited in Table II.

If method A is used, halogen-metal interconversion produces  $\phi_3\text{SiBr}$  which is then present along with excess  $\phi_3\text{SiK}$ . These compounds react slowly to give hexaphenyldisilane (II). In method B,  $\phi_3\text{SiBr}$  may again be formed, but only minute amounts of  $\phi_3\text{SiK}$  are present simultaneously, and, since the reaction is slow, no hexaphenyldisilane is isolated.

Triphenylsilanol (III) and hexaphenyldisiloxane (IV) may be considered together as hydrolysis products, arising from the hydrolysis of triphenylsilyl bromide. The ether is formed by an intermolecular dehydration of the silanol. These hydrolysis products are formed in larger yield via method B because a quantity of triphenylsilyl bromide accumulates for reasons cited in the preceding paragraph.

More benzene is formed in method A than in B because in method B the product formed more readily is biphenyl.

The presence of triphenylsilyl bromide has been strongly implicated by addition of a large excess of triphenylsilylpotassium in method B and subsequent isolation of a significant quantity of hexaphenyldisilane. The presence of phenylpotassium has been supported by addition of benzophenone and isolation of triphenylcarbinol.

Furthermore, in the reaction of triphenylsilylpotassium with chlorobenzene, triphenylsilyl chloride has been isolated in 5% yield.





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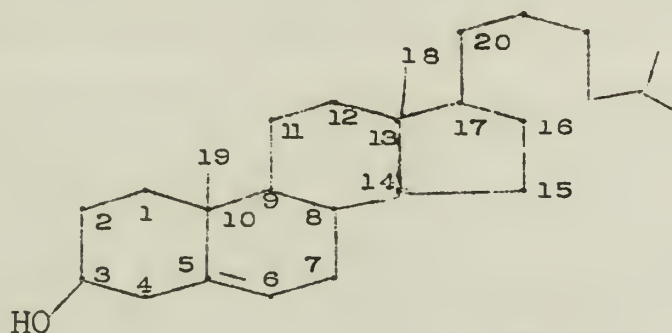


# TRANSMISSION OF ELECTRICAL EFFECTS IN THE CHOLESTERYL HOMOALLYLIC SYSTEM

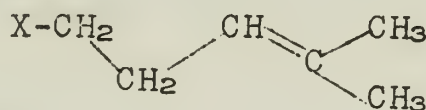
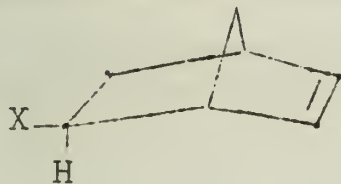
Reported by John A. Hedge

December 4, 1958

A homoallylic system is an allylic system with an interposed methylene group. Such a system is found in cholesterol, where the C<sub>4</sub>-

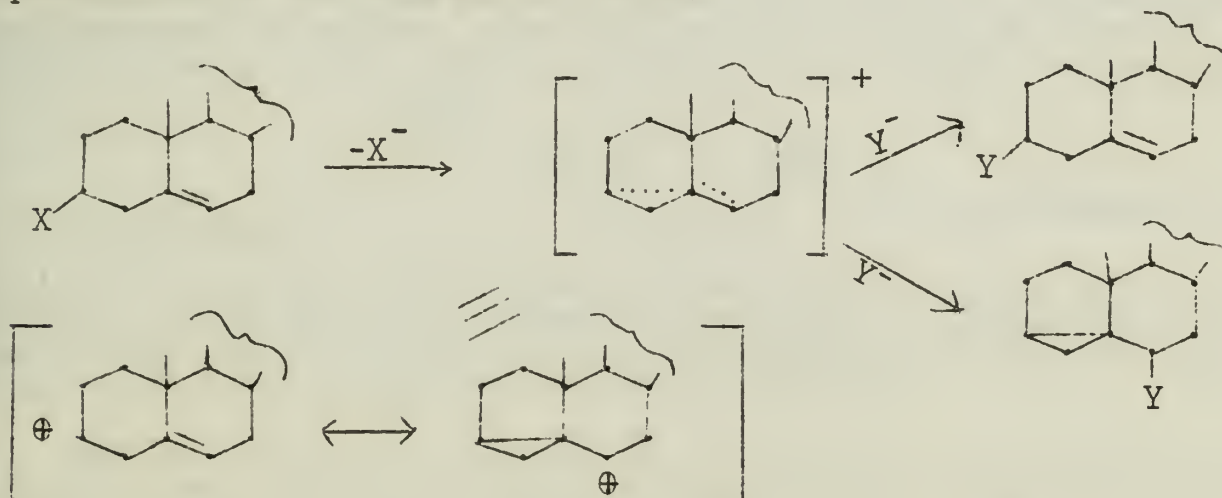


carbon is the interposed methylene group. Another example of a homoallylic system is found in dehydronorbornyl derivatives (1). Homoallylic behavior has been noted in a few simple aliphatic cases (2);



however, only steroids will be discussed in this report.

Reactions of the cholesteryl homoallylic system are proposed to proceed through the 3,5-cyclocholesteryl cation (3), which may be represented in two canonical forms.



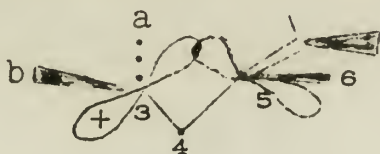
This cation can react at either C<sub>3</sub> or C<sub>6</sub> to give cholesteryl or i-cholesteryl (3,5-cyclocholestan-6-yl) products.

The mesomeric cation is stabilized by the 3,5-interaction of the





p-orbital at C<sub>5</sub> with what would have been a vacant C<sub>3</sub> p-orbital, resulting in a delocalization of the 5,6- $\pi$ -electron cloud (4,5). The



axes of the C<sub>3</sub> and C<sub>5</sub> p-orbitals lie in the same plane as C<sub>3</sub>, C<sub>4</sub>, and C<sub>5</sub>. Simonetta and Winstein (5) have calculated the energy of stabilization of the cation as 6 kcal/mole with a C<sub>3</sub>-C<sub>5</sub> distance of 1.75 to 1.95 Å. Shoppee (6), using a different C-C bond energy, has calculated a stabilization of 4-5 kcal/mole at ca. 2.1 Å.

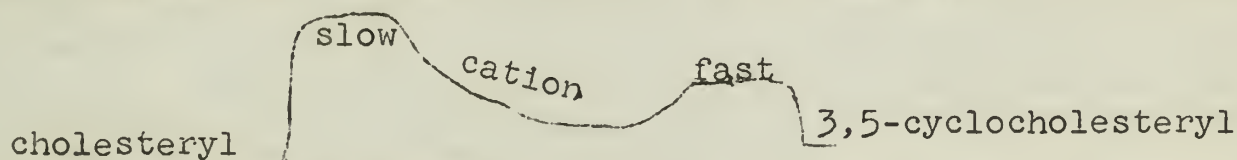
From the above orbital picture, one can see that the greatest electron density is on the  $\alpha$  side of the steroid. Thus, Dodson and Riegel (7) predicted that nucleophilic groups entering at C<sub>3</sub> or C<sub>6</sub> should enter from the  $\beta$  side. Most reactions of cholesteryl derivatives give retention of configuration. For example, cholesterol reacts with phosphorus pentachloride giving retention, whereas cholestanol (saturated) reacts with phosphorus pentachloride, giving the inverted  $\alpha$ -chloro derivative (8a,8b). Treatment of cholesteryl p-toluenesulfonate with LiAlD<sub>4</sub> gives the  $\beta$ -deutero product, while similar treatment of cholestanyl p-toluenesulfonate gives the inverted  $\alpha$ -deutero product (9). Many more examples of retention with nucleophilic reagents can be found.

It is interesting to note that acetylation of 7-oxocholesteryl chloride gives the inverted acetate (10). The C<sub>7</sub> carbonyl prevents



the  $\Delta^5$ -double bond from entering into the usual C<sub>3</sub>-C<sub>5</sub> interaction to form the mesomeric cation (11).

An energy diagram of the transformation of a cholesteryl compound, via a mesomeric cation, into a 3,5-cyclocholesteryl derivative is pictured below (12). Kinetic control should lead to the 3,5-cyclo



derivative, while thermodynamic control should give the  $\Delta^5$ -steroid product. From heats of formation and heats of combustion it has been found that the 3,5-cyclocholesteryl methyl ether is 5.7 kcal/mole less stable than the cholesteryl methyl ether (6).

The first kinetic studies on cholesteryl p-toluenesulfonate were done by Stoll (13). He found that cholesteryl tosylate ( $k = 0.18$ - $0.19$  min.<sup>-1</sup>) reacts 40 times as fast as cholestanyl tosylate ( $k = 0.46 \times 10^{-2}$  min.<sup>-1</sup>) in ethanol at 78°.

The acetolysis of cholesteryl tosylate was shown by Winstein and Adams (3) to proceed by first-order kinetics. Cholesteryl tosylate ( $k = 7.9 \times 10^{-3}$  min.<sup>-1</sup>) reacts at a rate ca. 100 times that of cyclohexyl

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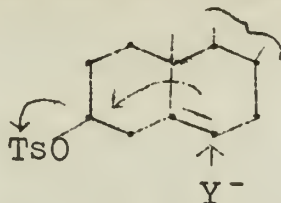
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tosylate ( $k = 0.111 \times 10^{-3} \text{ min.}^{-1}$ ) at  $50^\circ$ . The acetolysis rate extrapolated to  $78^\circ$  is  $0.176 \text{ min.}^{-1}$ , comparable with Stoll's 0.18-0.19  $\text{min.}^{-1}$ . Thus Stoll's reaction must have proceeded through the same cation, even though ethanol is much more likely to give an  $S_N2$  reaction. The fact that first-order kinetics were found eliminates the



possibility of a concerted mechanism. The rate enhancement by the pair of electrons of the ethylene group is analogous to neighboring group participation by aryl groups (3).

More recently a special salt effect in the acetolysis of cholesteryl tosylate was found by Winstein and Clippinger (27).

Wallis and his coworkers (14) found that the hydrolysis of various cholesteryl sulfonate esters in refluxing aqueous acetone with KOAc buffer is a first-order reaction. Rates were dependent on the C-O bond strengths, p-nitrobenzenesulfonate reacting fastest ( $k = 7.2 \times 10^{-4} \text{ sec}^{-1}$ ) and p-methoxybenzenesulfonate ( $k = 3.2 \times 10^{-4} \text{ sec}^{-1}$ ) reacting slowest of the sulfonates studied. The main product was i-cholesterol.

The isomerization of epi-i-cholesterol in dioxane and sulfuric acid gave cholesterol quantitatively. The reaction was found to be first-order in epi-i-cholesterol and first-order in acid, or second-order overall (15).

The methanolysis of cholesteryl p-toluenesulfonate in methanol: chloroform (10:1) with added methoxide ion is a first-order reaction with respect to tosylate ( $k = 0.43 \times 10^{-2} \text{ min}^{-1}$  at  $35^\circ$ ) (16). This rate is very close to the first-order rate constant of  $0.46 \times 10^{-2} \text{ min}^{-1}$  at  $34.8^\circ$  observed in methanol: chloroform (10:1) by Pearson, King and Langer (17). This shows that the methoxide ion is too weakly nucleophilic to compete with the homoallylic first-order reaction.

However, with very strong nucleophiles,  $S_N2$  inversion has been observed. The malonate anion reacts with cholesteryl tosylate to give ca.10% inverted ( $\alpha$ ) product (18,19,20,21). Methylamine (22), benzylamine (23), liquid ammonia (24), and dimethylamine (24,25) all give some inverted product when caused to react with cholesteryl tosylate or chloride. Thiophenoxide gives 13% 3  $\alpha$ -phenylthiocholest-5-ene, 32% 6  $\beta$ -phenylthio-3,5-cyclocholestane, and 8% 3,5-cyclocholest-6-ene. No 3 $\beta$ -phenylthiocholest-5-ene was found (26).

The isomerizations of 3,5-cyclocholestan-6 $\beta$ -yl and -6 $\alpha$ -yl trichloroacetates in benzene at  $25^\circ$  gave cholesteryl trichloroacetate ( $k = 1 \times 10^{-7}$  to  $10^{-6} \text{ sec}^{-1}$  for -6 $\beta$ -yl) (28a). Methanolysis of the 3,5-cyclocholestan-6 $\beta$ -yl and -6 $\alpha$ -yl trichloroacetates and of cholesteryl tosylate gave  $90 \pm 2\%$  of 3,5-cyclocholesteryl 6 $\beta$ -methyl ether and  $10 \pm 2\%$  of cholesteryl methyl ether, a fact which shows that there is a common intermediate. Hydrolysis of 3,5-cyclocholestan-6 $\beta$ -yl trichloroacetate in 90% dioxane gave cholesterol, i-cholesterol, and cholesteryl trichloroacetate. 3,5-Cyclocholestanyl-6 $\beta$ -chloride is ten times as reactive as the 6 $\alpha$ -chloride (28b).

The relative rate of solvolysis of ergosteryl tosylate is 30 times that of cholesteryl tosylate (5). This shows that the  $\Delta^7$ -double bond



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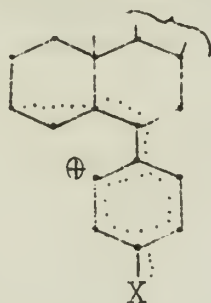
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is aiding in stabilization of the cationic intermediate. Hydrolysis of ergosteryl tosylate gives 3,5-cyclo-7,22-ergostadien-6 $\beta$ -ol (29). Since the  $\Delta^7$ -double bond does not migrate to the  $\Delta^6$  position in the product, the  $\Delta^7$ -double bond must aid the reaction in somewhat the same way as the  $\Delta^4$ -double bond of  $\psi$ -cholesteryl tosylate, which gives retention of the C<sub>7</sub> configuration but forms no 5,7-cyclo product in methanolysis (30). Dehydroergosteryl tosylate reacts more slowly than the ergosteryl analog, thus the 9(11)-double bond does not participate (29).

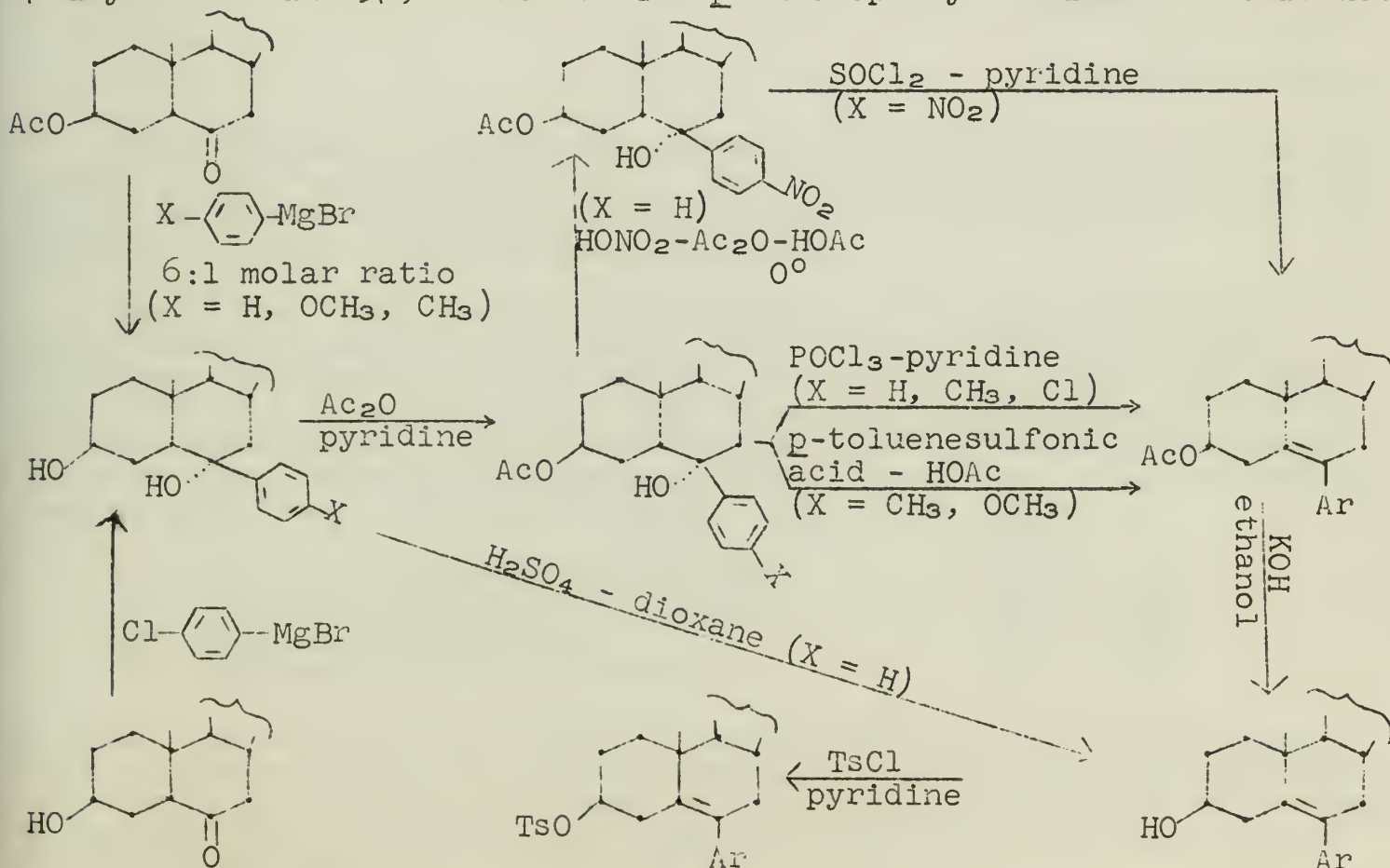
B-Norcholesteryl tosylate ( $k = 4.44 \times 10^{-3} \text{ min}^{-1}$ ) reacts about one-half as fast as cholesteryl tosylate ( $k = 7.75 \times 10^{-3} \text{ min}^{-1}$ ) [ $k = 7.9 \times 10^{-3} \text{ min}^{-1}$  (3)] in acetolysis at 50° (31).

All these reactions can be considered to involve a mesomeric cation as an intermediate. Stabilization of this cation should increase the reaction rate. Thus 6-alkyl or 6-aryl groups should help stabilize the cation as shown.



To test this, Sneen (32a) prepared five 6-arylcholesteryl tosylates and the 6-methylcholesteryl tosylate.

Cholestan-3 $\beta$ -ol-6-one acetate, prepared by the procedure of Dodson and Riegel (7), was caused to react with aryl Grignard reagents to give 6 $\beta$ -arylcholestane-3 $\beta$ ,6 $\alpha$ -diols. The *p*-chlorophenyl derivative could not







be made from the acetate and so was made from the  $3\beta$ -ol compound. The direct dehydration of  $6\beta$ -phenylcholestane- $3\beta,6\alpha$ -diol gave 6-phenyl cholesterol in poorer yields and purity than were obtained from dehydration and hydrolysis of the diol monoacetate.

The  $6\beta$  (axial) orientation was assigned to the  $6\beta$ -arylcholestane- $3\beta,6\alpha$ -diol monoacetates (32a). It would at first appear that  $\alpha$  attack by the Grignard reagent would be favored; but, when it is considered that the carbonyl oxygen is also coordinated with some magnesium species in the transition state, then the direction of attack becomes uncertain. The failure of  $6\beta$ -phenylcholestane- $3\beta,6\alpha$ -diol monoacetate to dehydrate in 8% HCl in refluxing ethanol is regarded as chemical proof for an equatorial 6-hydroxyl group.

Evidence for the  $6\beta$ -aryl configuration is afforded by a method of calculation of molecular rotation by J. H. Brewster, soon to be published. In the following table several observed and calculated values are given.

	<u>Obs.</u>	$[M]_D$	<u>Calcd.</u>
I Cholestanol	+93 (33)		-
II Cholestane- $3\beta,6\beta$ -diol	+57 (33)		+48
III Cholestane- $3\beta,6\alpha$ -diol	+154 (33)		+138
6 $\alpha$ -Phenylcholestane- $3\beta,6\beta$ -diol			+138 to +168 using I as basis.
			+147 to +177 using II as basis.
6 $\beta$ -Phenylcholestane- $3\beta,6\alpha$ -diol	+50 (32a)		+18 to +48 using I as basis.
			+34 to +64 using III as basis.

The synthesis of 6-methylcholesterol (32a) was similar to the syntheses of the 6-aryl derivatives. The tosylate could not be prepared from 6-methylcholesterol and so was prepared by treating the diol with *p*-toluenesulfonyl chloride and dehydrating.

Fieser and Rigaudy (35) have formulated the diol as  $6\alpha$ -methylcholestane- $3\beta,6\beta$ -diol on the basis of preferential Grignard attack (discussed earlier) and on molecular rotation comparisons. The substitution of a  $6\beta$ -methyl group (II) into cholestane- $3\beta,5\alpha$ -diol (I) increases levorotation. Since the 6-methyl diol (IV) was more dextro-rotatory than cholestane- $3\beta,6\beta$ -diol (III), Fieser and Rigaudy reasoned that it must have a  $6\alpha$ -methyl group.

	$[M]_D$
I Cholestane- $3\beta,5\alpha$ -diol	+81 (33)
II 6 $\beta$ -Methylcholestane- $3\beta,5\alpha$ -diol	-6.3 (35)
III Cholestane- $3\beta,6\beta$ -diol	+57 (33)
IV 6 $\alpha$ -Methylcholestane- $3\beta,6\beta$ -diol	+83 (35)

However, Sneen points out that the substitution of a 6-methyl group into a different parent compound, cholestane- $3\beta,6\alpha$ -diol (V), increases levorotation, and thus the methyl compound must be  $6\beta$ -methylcholestane- $3\beta,6\alpha$ -diol (VI). The  $6\beta$ -phenyl compound (VII) has a greater levorotation because the phenyl group is more polarizable.

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9. 10. 11. 12. 13. 14. 15. 16. 17. 18. 19. 20. 21. 22. 23. 24. 25. 26. 27. 28. 29. 30. 31. 32. 33. 34. 35. 36. 37. 38. 39. 40. 41. 42. 43. 44. 45. 46. 47. 48. 49. 50. 51. 52. 53. 54. 55. 56. 57. 58. 59. 60. 61. 62. 63. 64. 65. 66. 67. 68. 69. 70. 71. 72. 73. 74. 75. 76. 77. 78. 79. 80. 81. 82. 83. 84. 85. 86. 87. 88. 89. 90. 91. 92. 93. 94. 95. 96. 97. 98. 99. 100. 101. 102. 103. 104. 105. 106. 107. 108. 109. 110. 111. 112. 113. 114. 115. 116. 117. 118. 119. 120. 121. 122. 123. 124. 125. 126. 127. 128. 129. 130. 131. 132. 133. 134. 135. 136. 137. 138. 139. 140. 141. 142. 143. 144. 145. 146. 147. 148. 149. 150. 151. 152. 153. 154. 155. 156. 157. 158. 159. 160. 161. 162. 163. 164. 165. 166. 167. 168. 169. 170. 171. 172. 173. 174. 175. 176. 177. 178. 179. 180. 181. 182. 183. 184. 185. 186. 187. 188. 189. 190. 191. 192. 193. 194. 195. 196. 197. 198. 199. 200. 201. 202. 203. 204. 205. 206. 207. 208. 209. 210. 211. 212. 213. 214. 215. 216. 217. 218. 219. 220. 221. 222. 223. 224. 225. 226. 227. 228. 229. 230. 231. 232. 233. 234. 235. 236. 237. 238. 239. 240. 241. 242. 243. 244. 245. 246. 247. 248. 249. 250. 251. 252. 253. 254. 255. 256. 257. 258. 259. 260. 261. 262. 263. 264. 265. 266. 267. 268. 269. 270. 271. 272. 273. 274. 275. 276. 277. 278. 279. 280. 281. 282. 283. 284. 285. 286. 287. 288. 289. 290. 291. 292. 293. 294. 295. 296. 297. 298. 299. 300. 301. 302. 303. 304. 305. 306. 307. 308. 309. 310. 311. 312. 313. 314. 315. 316. 317. 318. 319. 320. 321. 322. 323. 324. 325. 326. 327. 328. 329. 330. 331. 332. 333. 334. 335. 336. 337. 338. 339. 340. 341. 342. 343. 344. 345. 346. 347. 348. 349. 350. 351. 352. 353. 354. 355. 356. 357. 358. 359. 360. 361. 362. 363. 364. 365. 366. 367. 368. 369. 370. 371. 372. 373. 374. 375. 376. 377. 378. 379. 380. 381. 382. 383. 384. 385. 386. 387. 388. 389. 390. 391. 392. 393. 394. 395. 396. 397. 398. 399. 400. 401. 402. 403. 404. 405. 406. 407. 408. 409. 410. 411. 412. 413. 414. 415. 416. 417. 418. 419. 420. 421. 422. 423. 424. 425. 426. 427. 428. 429. 430. 431. 432. 433. 434. 435. 436. 437. 438. 439. 440. 441. 442. 443. 444. 445. 446. 447. 448. 449. 450. 451. 452. 453. 454. 455. 456. 457. 458. 459. 460. 461. 462. 463. 464. 465. 466. 467. 468. 469. 470. 471. 472. 473. 474. 475. 476. 477. 478. 479. 480. 481. 482. 483. 484. 485. 486. 487. 488. 489. 490. 491. 492. 493. 494. 495. 496. 497. 498. 499. 500. 501. 502. 503. 504. 505. 506. 507. 508. 509. 510. 511. 512. 513. 514. 515. 516. 517. 518. 519. 520. 521. 522. 523. 524. 525. 526. 527. 528. 529. 530. 531. 532. 533. 534. 535. 536. 537. 538. 539. 540. 541. 542. 543. 544. 545. 546. 547. 548. 549. 550. 551. 552. 553. 554. 555. 556. 557. 558. 559. 560. 561. 562. 563. 564. 565. 566. 567. 568. 569. 570. 571. 572. 573. 574. 575. 576. 577. 578. 579. 580. 581. 582. 583. 584. 585. 586. 587. 588. 589. 590. 591. 592. 593. 594. 595. 596. 597. 598. 599. 600. 601. 602. 603. 604. 605. 606. 607. 608. 609. 610. 611. 612. 613. 614. 615. 616. 617. 618. 619. 620. 621. 622. 623. 624. 625. 626. 627. 628. 629. 630. 631. 632. 633. 634. 635. 636. 637. 638. 639. 640. 641. 642. 643. 644. 645. 646. 647. 648. 649. 650. 651. 652. 653. 654. 655. 656. 657. 658. 659. 660. 661. 662. 663. 664. 665. 666. 667. 668. 669. 670. 671. 672. 673. 674. 675. 676. 677. 678. 679. 680. 681. 682. 683. 684. 685. 686. 687. 688. 689. 690. 691. 692. 693. 694. 695. 696. 697. 698. 699. 700. 701. 702. 703. 704. 705. 706. 707. 708. 709. 710. 711. 712. 713. 714. 715. 716. 717. 718. 719. 720. 721. 722. 723. 724. 725. 726. 727. 728. 729. 730. 731. 732. 733. 734. 735. 736. 737. 738. 739. 740. 741. 742. 743. 744. 745. 746. 747. 748. 749. 750. 751. 752. 753. 754. 755. 756. 757. 758. 759. 760. 761. 762. 763. 764. 765. 766. 767. 768. 769. 770. 771. 772. 773. 774. 775. 776. 777. 778. 779. 780. 781. 782. 783. 784. 785. 786. 787. 788. 789. 790. 791. 792. 793. 794. 795. 796. 797. 798. 799. 800. 801. 802. 803. 804. 805. 806. 807. 808. 809. 810. 811. 812. 813. 814. 815. 816. 817. 818. 819. 820. 821. 822. 823. 824. 825. 826. 827. 828. 829. 830. 831. 832. 833. 834. 835. 836. 837. 838. 839. 840. 841. 842. 843. 844. 845. 8

|     |   | Obs. | $[M]_D$ | Calcd.     |
|-----|---|------|---------|------------|
| V   | Cholestane- $3\beta,6\alpha$ -diol                  | +154 | (33)    |            |
| VI  | 6 $\beta$ -Methylcholestane- $3\beta,6\alpha$ -diol | +83  | (35)    | +78 to +94 |
| VII | 6 $\beta$ -Phenylcholestane- $3\beta,6\alpha$ -diol | +50  | (32a)   |            |

Calculation by Brewster's method also shows the methyl group to be 6 $\beta$ .

The solvolysis of the six cholesteryl tosylates was studied in 90 volume per cent aqueous dioxane with a slight excess of LiOAc to react with the *p*-toluenesulfonic acid formed during solvolysis (32b,32c). Titrimetric rates were checked polarimetrically in the case of the methyl and *p*-chlorophenyl compounds. All the tosylates showed fair to good first-order kinetics. The results are given in the following table.

Solvolysis in 90 Volume Per Cent Aqueous Dioxane

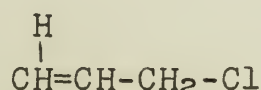
| <i>p</i> -Toluenesulfonate           | $[ROTs]$<br>$\times 10^2$ | $k \times 10^6 \text{ sec}^{-1}$ | Temp.<br>$^{\circ}C.$ | Relative<br>Rate |
|--------------------------------------|---------------------------|----------------------------------|-----------------------|------------------|
| Cholestanyl                          |                           | 0.154*                           | 50                    | 1.00             |
| 6- <i>p</i> -Nitrophenylcholesteryl  | 1.10                      | $1.26 \pm .09$                   | 50                    | 8.2              |
| 6- <i>p</i> -Chlorophenylcholesteryl | 0.916                     | $2.81 \pm .16$                   | 50                    | 18.2             |
|                                      | 1.50                      | $2.77 \pm .33$                   | 50                    |                  |
| 6-Phenylcholesteryl                  | 1.09                      | $5.79 \pm .10$                   | 50                    | 37.6             |
|                                      | 1.49                      | $73.7 \pm 1.7$                   | 75.1                  |                  |
| 6- <i>p</i> -Tolylcholesteryl        | 1.53                      | $8.34 \pm .22$                   | 50                    | 54.0             |
| 6- <i>p</i> -Anisylcholesteryl       | 1.05                      | $14.4 \pm .3$                    | 50                    |                  |
|                                      | 1.52                      | $14.0 \pm .7$                    | 50                    | 91.0             |
|                                      | 0.867                     | $13.4 \pm .4$                    | 50                    |                  |
| Cholesteryl                          | 1.26                      | $18.0 \pm .2$                    | 50                    |                  |
|                                      | 1.53                      | $18.3 \pm .4$                    | 50                    | 118              |
|                                      | 1.46                      | $18.3 \pm .3$                    | 50                    |                  |
| 6-Methylcholesteryl                  |                           | **1360                           | 50                    | 8,840            |

\*extrapolated from glacial acetic acid.

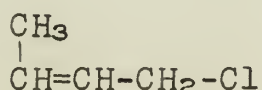
\*\*extrapolated from rates at lower temperatures.

$\beta$ -Phenyl groups have an inductive (-I) effect which has been estimated to retard rates by a factor of 8 to 10 (36,37). Thus unassisted ionization rates of the arylcholesteryl tosylates would be expected to be slower than for cholestanyl tosylate. Therefore, all the 6-aryl tosylates undergo some degree of anchimerically assisted ionization by way of the mesomeric cholesteryl cation. The very much enhanced rate of the methylcholesteryl derivative is evidence for a high degree of assistance. The methyl group significantly stabilizes the transition state ( $\Delta\Delta F^* = 2.69 \text{ kcal}$ ).

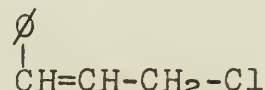
The kinetic results show that even the *p*-methoxyphenyl analog is only 0.77 times as reactive as the hydrogen analog (cholesteryl), while the methyl analog reacts 74.8 times faster than cholesteryl and 235 times faster than 6-phenylcholesteryl tosylate. In the allylic system relative rates are (38):



1.00



95



8800





Thus in the homoallylic system the 6-methyl derivative shows about the expected rate enhancement, while the 6-aryl derivatives show definitely "abnormal" rate enhancement.

This "abnormal" effect of the arylcholesteryl tosylates can be attributed to (32c) (a) combined inductive effects of the  $\Delta^5$ -double bond and the 6-aryl group; (b) non-bonded steric interactions between the aryl group and the approaching atoms of the incipient three-membered ring, causing steric inhibition of resonance or lengthening the C<sub>3</sub>-C<sub>5</sub> bond in the transition state, decreasing the stabilization due to electron overlap; and (c) greater stabilization of the 6-arylcholesteryl tosylate than of the transition state by conjugation of the aryl group and the C<sub>5</sub>-C<sub>6</sub> double bond (just as the conjugated C<sub>7</sub> carbonyl allows inversion at C<sub>3</sub>) (10,11).

Sneen (32b) has applied the Hammett equation to the 6-arylcholesteryl homoallylic system. Using  $\sigma$  values, where *p*-methyl, *p*-chloro, and *p*-hydrogen fit best, a  $\rho$  of -0.962 ( $\pm$  0.095) is obtained. Using  $\sigma^+$  values (39), where *p*-methoxy fits best, a  $\rho$  of -0.705 ( $\pm$  0.10) is obtained.

|                    | $\sigma$ | $\sigma^+$ (39) |
|--------------------|----------|-----------------|
| <i>p</i> -nitro    | + 0.778  | + 0.777         |
| <i>p</i> -chloro   | + 0.226  | + 0.112         |
| <i>p</i> -hydrogen | 0.00     | 0.00            |
| <i>p</i> -methyl   | - 0.170  | - 0.306         |
| <i>p</i> -methoxy  | - 0.268  | - 0.764         |

A study of benzyl tosylate solvolysis in 76.6 mole per cent aqueous acetone at 25.3° gave a  $\rho$  value of -2.20  $\pm$  0.07 (40). This shows that the homoallylic system is less sensitive than the benzyl system. The same factors which decrease the rate of solvolysis also decrease the sensitivity (32b).

Sneen made only a preliminary examination of the solvolysis products (32b). 6-Phenylcholesteryl tosylate gave 6-phenylcholesterol in 73% yield. A quenched reaction mixture of 6-*p*-chlorophenylcholesteryl tosylate precipitated directly 48% of 6-*p*-chlorophenylcholesterol.

The first-order polarimetric rates show that the alcohol of retained configuration is a primary product. An unstable initial product should reveal itself in a drifting polarimetric rate constant. However, an extremely unstable product, which rearranges at a rate much faster than the rate-determining solvolysis step, is possible. Thus, 6 $\alpha$ -aryl-3,5-cyclocholestan-6 $\beta$ -ols cannot be ruled out as unstable intermediates.





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## CATALYTIC OXIDATION IN AQUEOUS SOLUTION

Reported by E. Thomas Niles

December 8, 1958

Catalytic oxidation with molecular oxygen has attained great commercial importance. Paraffinic hydrocarbons are oxidized to fatty acids, and alcohols are oxidized to aldehydes, ketones and acids by the use of a variety of different metals, metallic oxides and metallic salts. For the most part, catalytic oxidation is applied in the gas phase. Strecker (1) was the first to mention that platinum catalyst in the presence of air catalyzes oxidation. The use of aqueous solutions was described later by Gorup-Besanez (2) and Dafert (3), who found that a reducing material (mannose) and a solid acid (mannonic acid) were formed when a solution of mannitol with platinum black was stirred in air. Catalytic oxidation as presented here is a mild, selective, quantitative laboratory method of oxidizing hydroxyl groups in a variety of different compounds. The value of catalytic oxidation in aqueous solution lies in its selectivity.

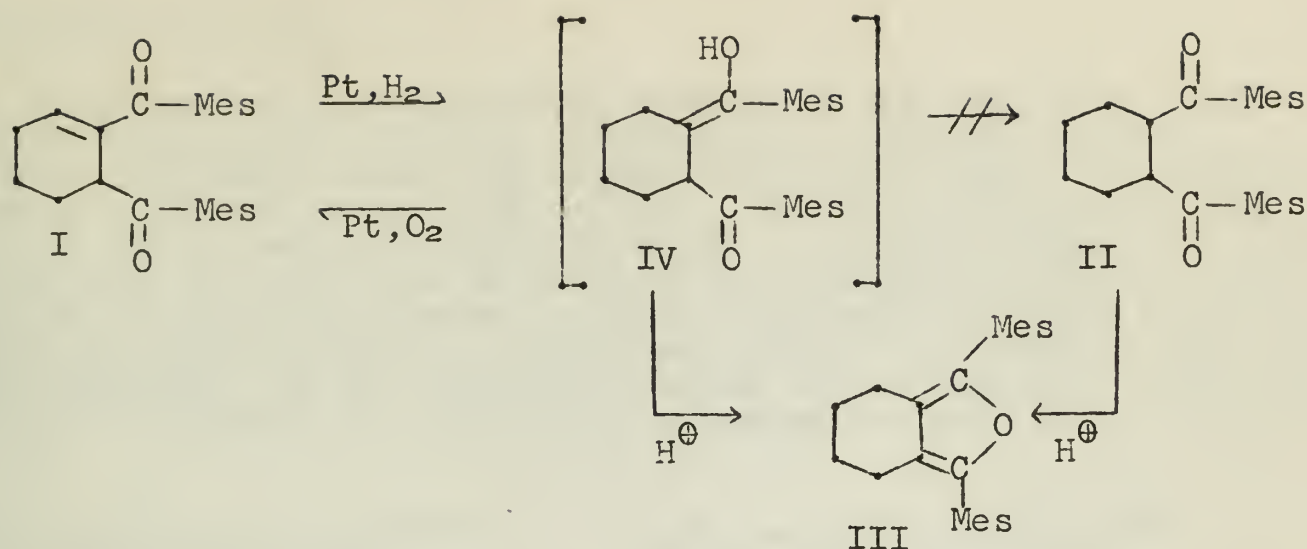
### THEORETICAL CONSIDERATIONS

Wieland (4) produced aldehydes and acids from alcohols in aqueous solution by the use of platinum and air. He described the reaction as dehydrogenation, in which the platinum activates the alcohol and the molecular oxygen serves as the acceptor for the activated hydrogen. He found that oxidation could be carried out in the absence of oxygen if other acceptors were used such as methylene blue or quinone, and assumed the mechanism to be analogous to that of enzymatic oxidation. Several sets of workers have supported the dehydrogenation theory. Müller and Schwabe (5) carried out quantitative experiments measuring the potential of the platinum catalyst during oxidation. They found that at the beginning of the oxidation the platinum catalyst electrode acquires a potential due to adsorbed hydrogen. As the uptake of oxygen decreases, indicating the end of oxidation, the potential of the catalyst becomes more oxidizing and acquires the potential of oxygen. This shows that the adsorbed hydrogen is oxidized on the surface of the catalyst. Macrae (6) has postulated that the hydrogen adsorbed on the metal surface is oxidized by the oxygen to hydrogen peroxide, which decomposes rapidly into water and oxygen. He detected the presence of hydrogen peroxide as the colored ceric hydroperoxide which could be estimated iodimetrically. It is not clear whether the hydrogen peroxide plays any further part in oxidation.

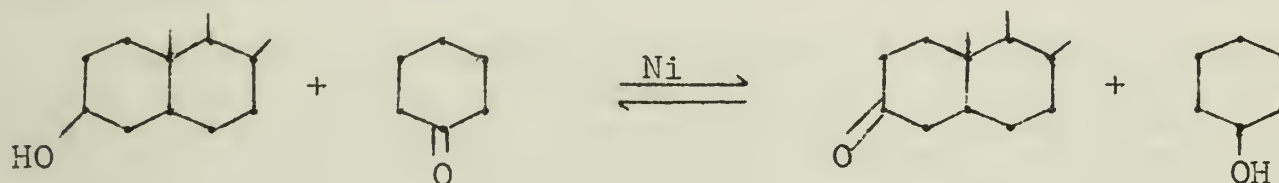
A reaction which illustrates the similarity between hydrogenation and oxidation (dehydrogenation) in the presence of platinum is the hydrogenation of 1,2-dimesityl-2-cyclohexene (7).







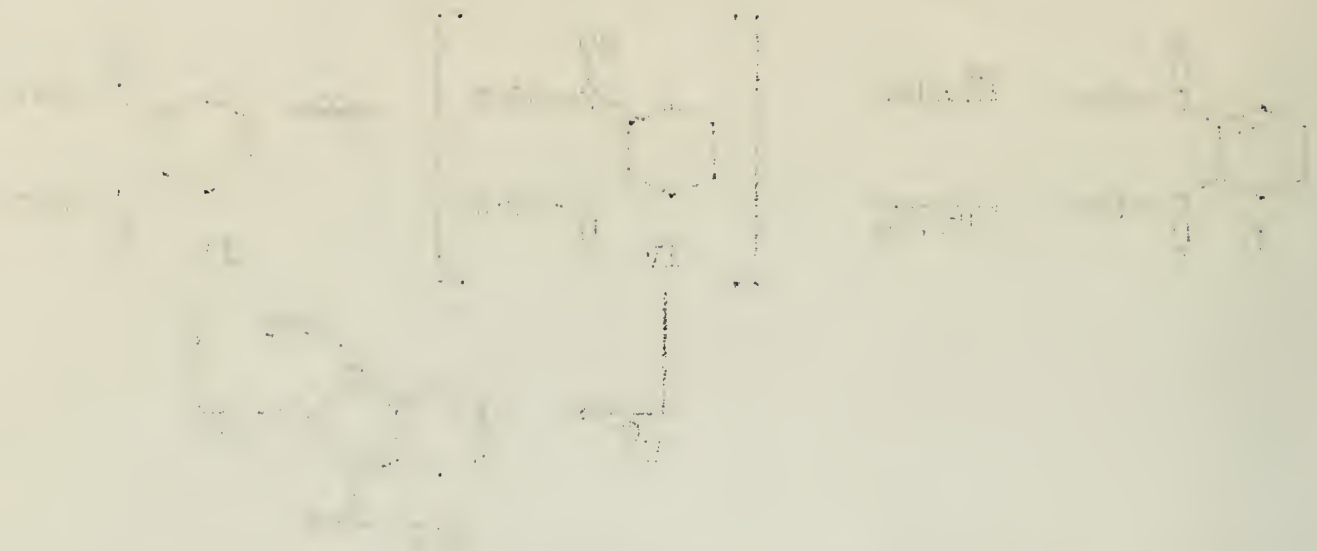
Kleiderer and Kornfeld (44) used nickel as an oxidation and reduction catalyst. By refluxing dihydrocholesterol in cyclohexanone with Raney nickel for 24 hours, cholestanone was produced in 80% yield. Cyclohexanone acted as the oxygen acceptor. The reverse



reaction was also carried out; thus, after refluxing cholestanone for 22 hours in cyclohexanol with nickel, dihydrocholesterol (50%) was obtained.

## ALCOHOLS

Aliphatic as well as aromatic alcohols can be oxidized to acids in aqueous solution. The time and temperature required for complete (ca. 100%) oxidation increase with the size of the alcohol; for example, by stirring in air with Adams catalyst, ethanol can be oxidized to acetic acid in 1.5 hours at  $22^\circ$ , 1-propanol to propionic acid in 17 hours at  $20^\circ$ , while 1-butanol takes over 20 hours at  $80^\circ$  to go to the acid. 2-Propanol is oxidized to acetone under the same conditions of time and temperature that are required to oxidize 1-propanol. However, higher secondary alcohols are difficult to oxidize in aqueous solution because of their insolubility. The insoluble alcohols tend to coagulate the platinum catalyst and the reaction ceases (8). Because of this insolubility in water, Sneed and Turner (9) investigated the use of organic solvents. The best yields were obtained in ethyl acetate or aqueous acetone, while poorer yields resulted when acetic acid or dimethylformamide was used as a solvent. Caproaldehyde, benzaldehyde, and cyclohexanone were obtained (as 2,4-dinitrophenylhydrazones) in 21%, 72%, and 68% yields, respectively, in ethyl acetate as the solvent with Adams catalyst. Heyns and Paulsen (8), using benzene and dioxane as solvents, oxidized 2-hexanol, 2-octanol, and 2-decanol catalytically to ketones; the rate of oxidation decreased with increasing chain length.



The reaction of (1) with (2) was carried out in the presence of a catalyst. The reaction mixture was stirred at room temperature for 24 hours. The product (3) was isolated by extraction with ether and dried over anhydrous sodium sulfate. The yield of (3) was 85%.



The reaction of (6) with mCPBA was carried out in dichloromethane at 0°C. The reaction mixture was stirred for 2 hours. The product (7) was isolated by extraction with ether and dried over anhydrous sodium sulfate. The yield of (7) was 90%.

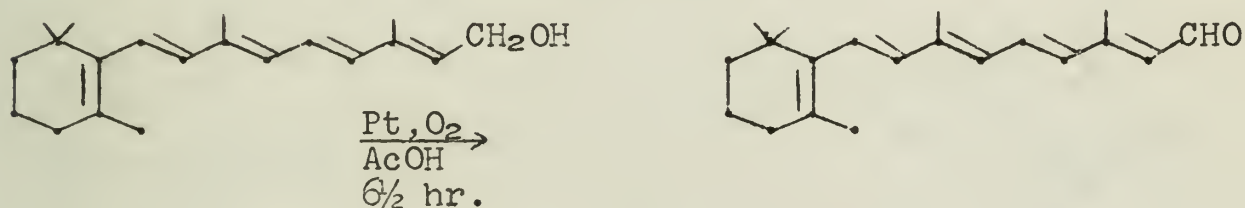
ANAL.

Calcd for C<sub>10</sub>H<sub>16</sub>O: C, 85.71%; H, 11.43%. Found: C, 85.6%; H, 11.5%. IR (KBr): 1715 (C=O), 1640 (C=C), 1450 (C-O), 1380 (C-O), 1280 (C-O), 1100 (C-O), 1050 (C-O), 1000 (C-O), 950 (C=C), 900 (C=C), 850 (C=C), 800 (C=C), 750 (C=C), 700 (C=C), 650 (C=C), 600 (C=C), 550 (C=C), 500 (C=C), 450 (C=C), 400 (C=C), 350 (C=C), 300 (C=C), 250 (C=C), 200 (C=C), 150 (C=C), 100 (C=C). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.1 (s, 1H), 6.8 (s, 1H), 6.5 (s, 1H), 6.2 (s, 1H), 5.9 (s, 1H), 5.6 (s, 1H), 5.3 (s, 1H), 5.0 (s, 1H), 4.7 (s, 1H), 4.4 (s, 1H), 4.1 (s, 1H), 3.8 (s, 1H), 3.5 (s, 1H), 3.2 (s, 1H), 2.9 (s, 1H), 2.6 (s, 1H), 2.3 (s, 1H), 2.0 (s, 1H), 1.7 (s, 1H), 1.4 (s, 1H), 1.1 (s, 1H), 0.8 (s, 1H), 0.5 (s, 1H), 0.2 (s, 1H).



## UNSATURATED ALCOHOLS

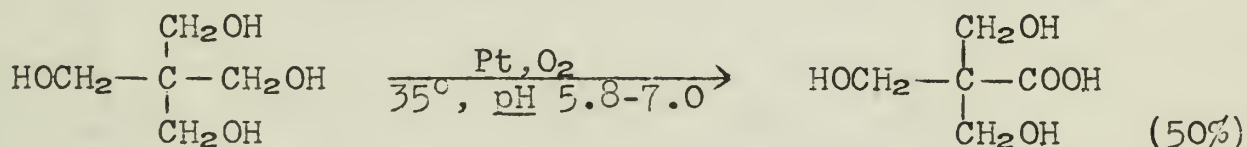
There are very few recorded examples of the catalytic oxidation of unsaturated alcohols. Strecker (1) oxidized cinnamyl alcohol to cinnamic acid, and Delaby (10) found that allyl alcohol could be oxidized to acrolein at 80°. Air was bubbled into the alcohols which contained platinum black. A recent example is found in the work of Karrer and Hess (11), who oxidized vitamin A to the aldehyde at room temperature in acetic acid with one-half mole of oxygen and Adams catalyst. Manganese dioxide was formerly used for this oxidation, but the reaction carried out in petroleum ether took 78 days. Catalytic oxidation gave comparable yields in 6.5 hours.



## POLYALCOHOLS

Some years ago Glattfeld and Gershon (12) oxidized compounds in the hexitol series using Adams catalyst. The oxidation of mannitol produced sugars. The configuration of the oxidation product depends on whether the primary hydroxyl on C<sub>1</sub> or C<sub>6</sub> is oxidized. Further oxidation leads to a mixture of D-mannonic acid, D-mannuronic acid and D-mannosaccharonic acid. Similar products were obtained from dulcitol. Recently, Heyns and Beck (13) oxidized D-sorbitol in the presence of platinum-carbon catalyst and obtained a mixture of D-glucose, D-fructose, L-gulose and L-sorbose. They showed that acetic acid solutions favor aldose over ketose formation.

Pentaerythritol in weak acid or neutral solution can be selectively oxidized in the presence of platinum catalyst to tris-(hydroxymethyl)acetic acid, which is stable to further oxidation (14). With potassium hydroxide at higher temperatures, bis-



(hydroxymethyl)malonic acid was detected by paper chromatography; oxalic acid has not been found.

The effect of chain length or molecular weight on oxidation time has been noted in polyalcohols (8). Ethylene glycol is oxidized to the mono-acid in the presence of one mole of alkali in 11 hours at 95°, while the oxidation of 1,4-butanediol takes 32 hours at the same temperature.

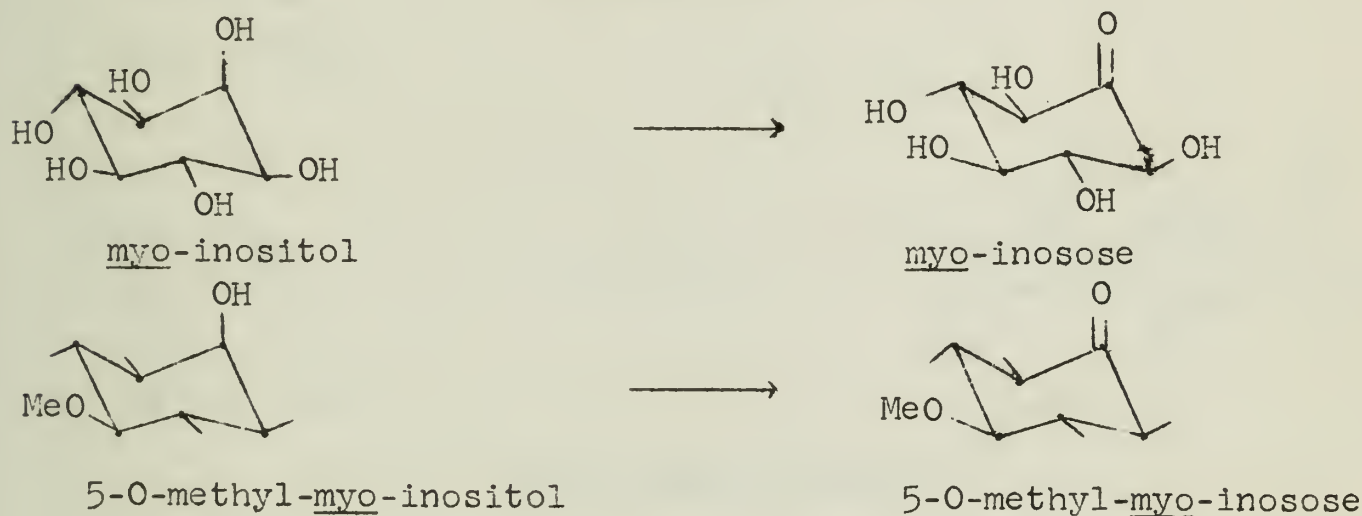


# CYCLITOLS

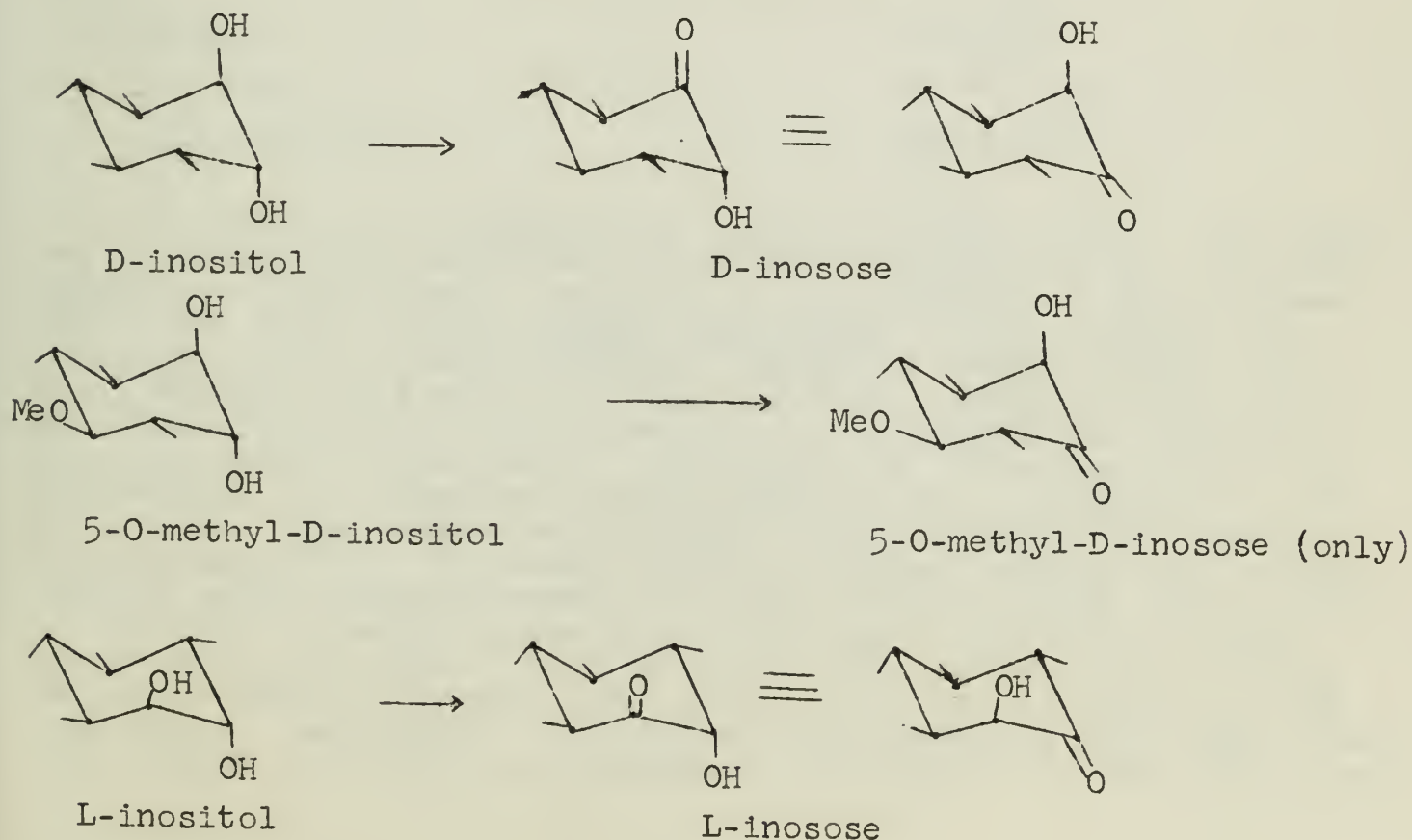
## Inositols

In the hexahydroxycyclohexanes, inositols, catalytic oxidation is remarkably selective. A secondary hydroxyl group which is axial is oxidized to a keto function, leaving the equatorial hydroxyl groups intact. This selectivity was first noted by Heyns and Paulsen (8,15), and has been confirmed by other workers (16,17). The selective nature of the oxidation of inositol stereoisomers is shown in the following reactions.

### One axial OH group

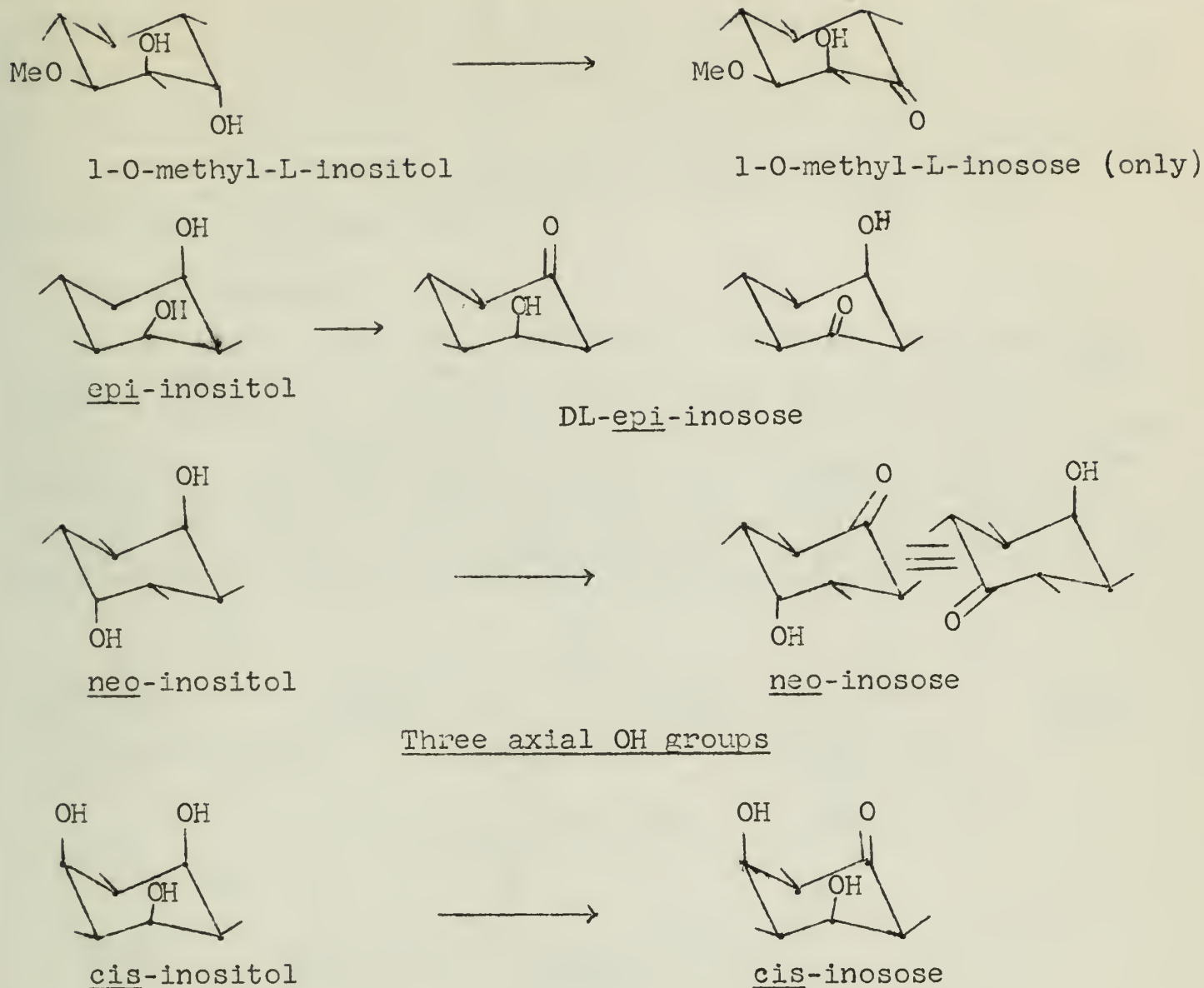


### Two axial OH groups









In contrast to permanganate oxidation, which cleaves the ring, and to nitric acid oxidation, which gives DL-epi-inosose, catalytic oxidation of myo-inositol results in the formation of myo-inosose (15). The action of Acetobacter suboxidans on myo-inositol also gives myo-inosose (28). Catalytic oxidation of myo-inositol in basic solution does result in ring cleavage producing oxalic acid and other carboxylic acids; however, as the acidity is increased, fewer by-products are formed. At pH 3.5, if the oxidation is carried out for 3 hours at 70-75°, myo-inosose is produced in 78% yield (15). myo-Inosose was reduced to myo-inositol and scyllitol by Posternak (45). He obtained about an equal mixture with sodium-amalgam as the reducing agent, but with Adams catalyst and one mole of hydrogen in neutral aqueous solution myo-inositol was formed exclusively with only a trace of scyllitol. Inositol, possessing two axial hydroxyl groups, gave only a mono-ketone; thus in D and L-inositol oxidation of either axial hydroxyl group gave the same product. Little or no diketone was formed. On the other hand,

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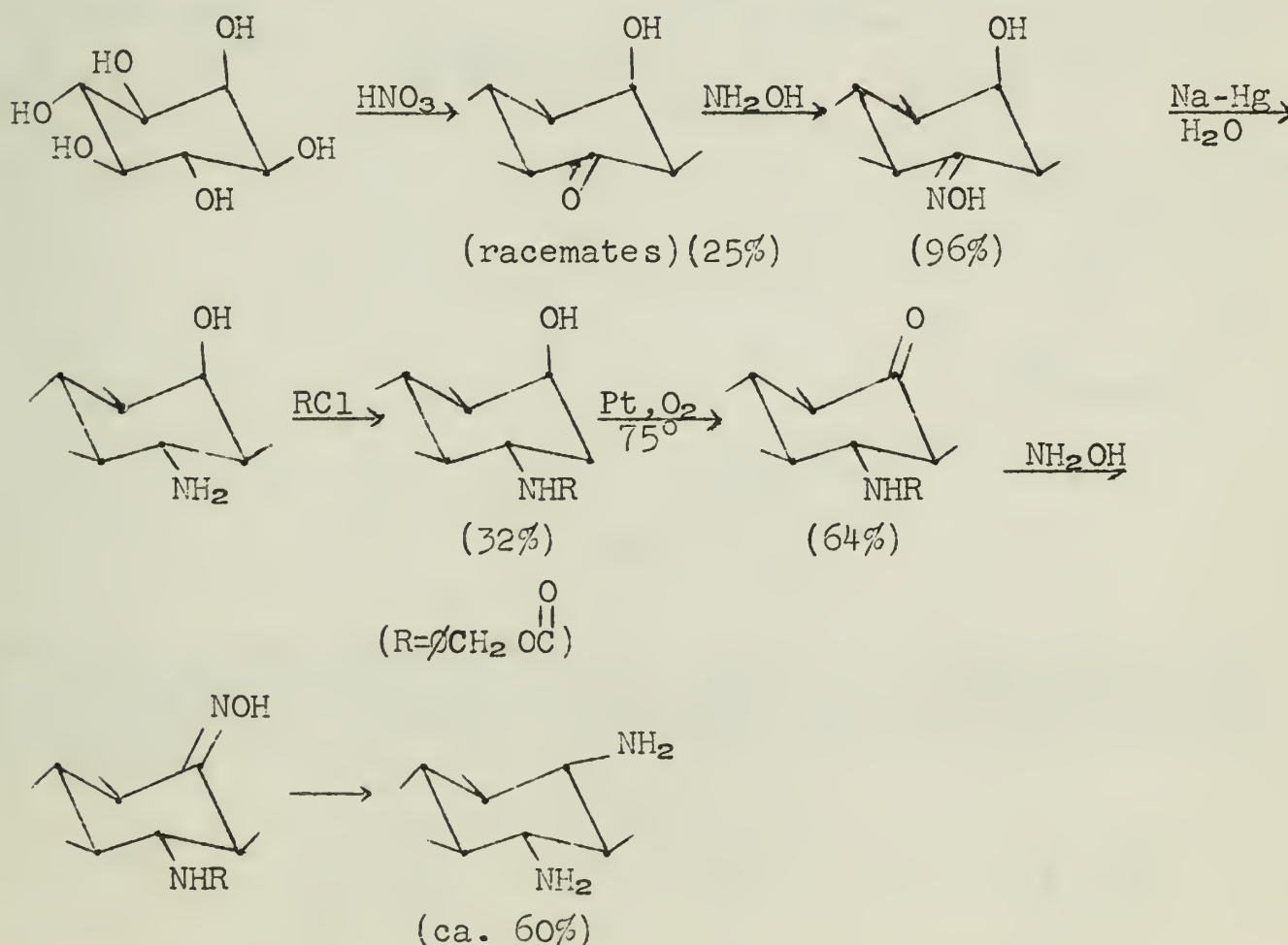
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the 1-O-methyl and 5-O-methyl derivatives have axial hydroxyl groups which are not equivalent, and further selectivity is exhibited (18). In each instance the axial group which was less hindered by the methoxy group was oxidized forming only one inosose. Catalytic oxidation of epi-inositol results in racemic epi-inosose (8). Of the inositols which have three axial hydroxyl groups, oxidation has been carried out only on cis-inositol (8), giving cis-inosose. Scyllitol, which has only equatorial hydroxyl groups, is not catalytically oxidized (8).

### Amino Cyclitols

Heyns and Paulsen (18) catalytically oxidized N-carbobenzoxy-DL-myo-inosamine to N-carbobenzoxy-DL-2-keto-myo-inosamine. This reaction shows that selectivity toward axial hydroxyl groups applies also to amine derivatives. The usefulness of this reaction is seen in their synthesis of streptamine from myo-inositol. The carbobenzoxy group was used to protect the sensitive amino group. The free amine was obtained upon final reduction with sodium-amalgam. The yield in the oxidation step was increased by 50% when Adams catalyst was used in place of platinum-on-carbon.

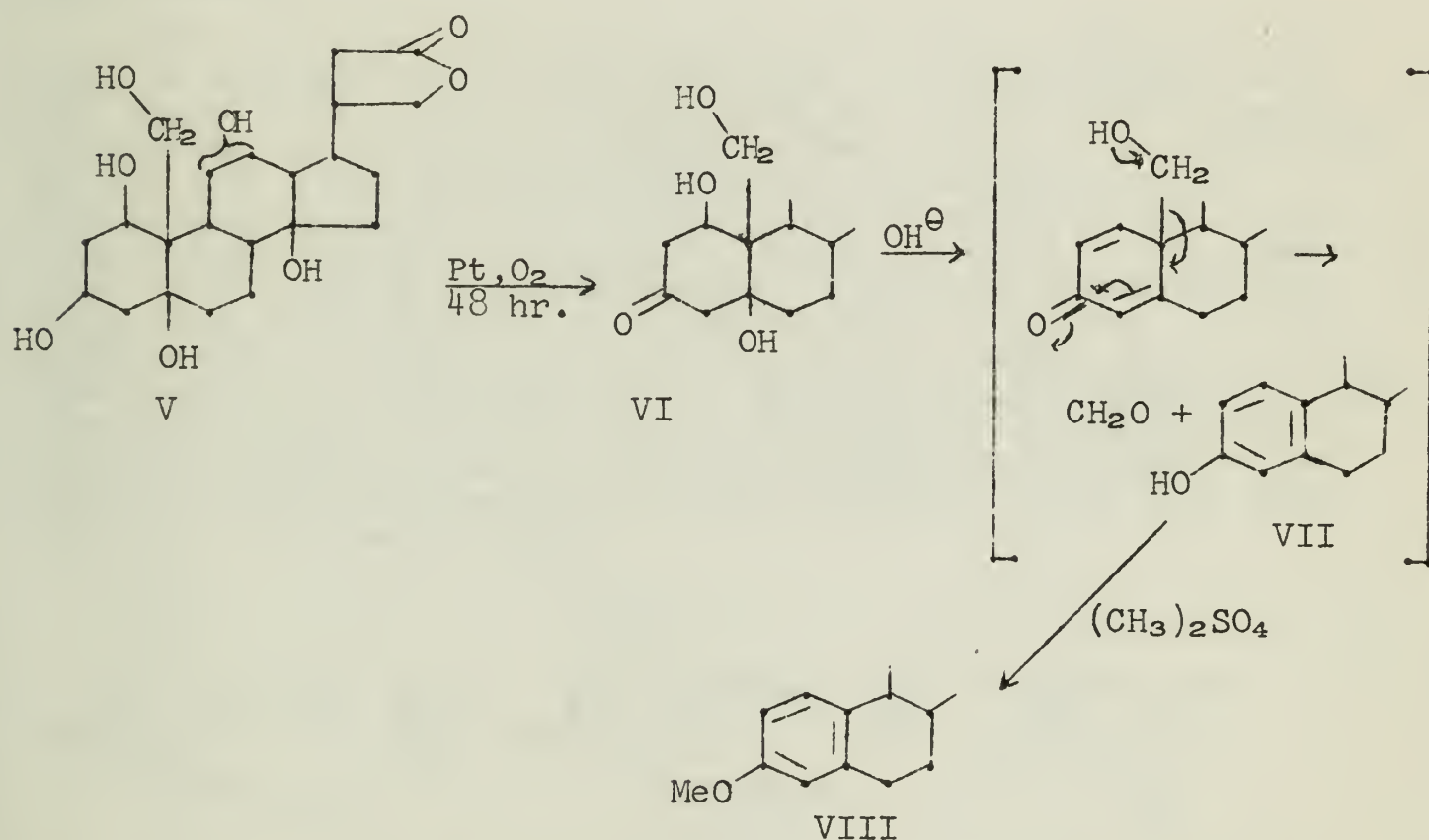


### STERIODS

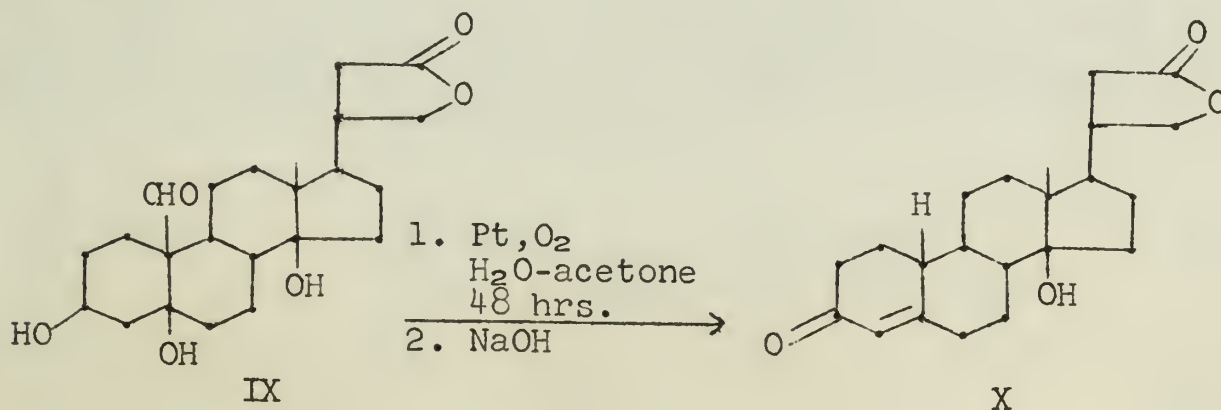
Selectivity between axial and equatorial hydroxyls in steroid systems is not as great as it is in cyclitols. In almost every instance the hydroxyl group on C<sub>3</sub> is much more easily oxidized than other hydroxyl groups in the steroid nucleus. This is true in



A/B-cis- and A/B-trans-fused steroids (19). Sneed and Turner catalytically oxidized 3 $\alpha$ -cholestanol and 3 $\beta$ -cholestanol to 3-cholestanone (50% and 72% yields) (9,20). In the series of bile esters -- methyl 3 $\alpha$ -hydroxycholestanate, methyl 3 $\alpha$ , 6 $\alpha$ -dihydroxycholestanate, methyl 3 $\alpha$ , 12 $\alpha$ -dihydroxycholestanate and methyl 3 $\alpha$ , 7 $\alpha$ , 12 $\alpha$ -trihydroxycholestanate -- 3-keto derivatives were produced in 70-75% yield (9). The hydroxyl group at C<sub>3</sub> is oxidized selectively even in the presence of a primary hydroxyl group at C<sub>19</sub>, as illustrated in the oxidation of 20,21-dihydro $\beta$ uabagenin (V). Here, Sneed and Turner (20) obtained about 80% of the corresponding 3-keto compound (VI). Under basic conditions this compound appeared to undergo  $\beta$ -elimination and reverse aldol cleavage to yield formaldehyde and VII, which was isolated as the methyl ether (VIII).



Similarly, Turner and Meschino (21) carried out the oxidation of 20, 21-dihydrostrophanthidin (IX). The 3-keto compound was not isolated, but upon treatment with sodium hydroxide the product X was obtained.





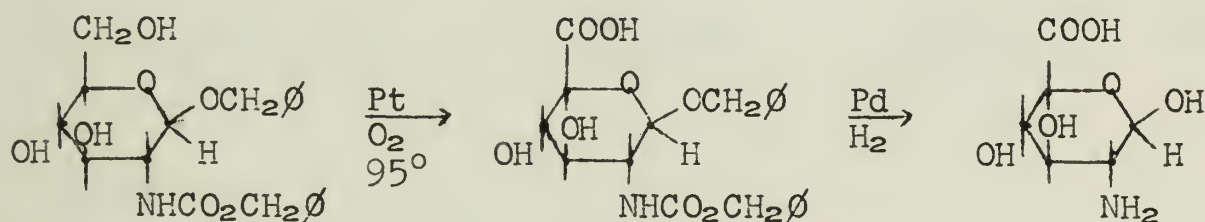


## ALDOSES

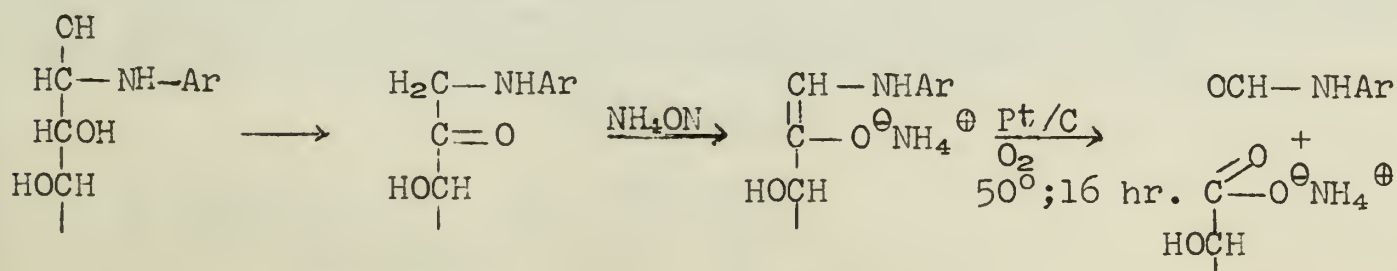
Using a palladium catalyst (Pd-on-CaCO<sub>3</sub>), Busch (22) found that D-glucose could be oxidized to D-gluconic acid. Further oxidation did not yield saccharic acid, but rather the gluconic acid decomposed stepwise, starting at C-1, to give arabonic, erythronic, tartaric, tartronic and oxalic acids, and CO<sub>2</sub> (23). Platinum-on-carbon (24) and palladium-on-manganese oxide (23) have also been used for the preparation of gluconic acid. D-Glucose has been oxidized in 12.5 hours to D-saccharic acid (54% as potassium salt) with platinum-activated carbon catalyst at pH 5.0-9.6 (25). The oxidation of pentoses is very rapid compared with that of hexoses. In 45 minutes at 50° L-arabinose is oxidized to the acid in 95% yield (25).

## AMINO SUGARS

Heyns and Kock (31) found that D-glucosamine hydrochloride could be oxidized under mild conditions to 2-aminogluconic acid (37% yield). The reaction was carried out at 30°, and potassium bicarbonate was continuously added to keep the pH at 7. Heyns and Paulsen (33) found that by blocking the amino group with a carbobenzoxy group and the aldehyde portion with a benzyl ether, 2-amino-2-deoxy-D-glucose could be oxidized easily to the uronic acid. The blocking groups are easily removed by hydrogenation. Benzyl-N-carbobenzoxy-D-glucosamide is quite insoluble, and the oxidation must be carried out in suspension, whereby the acid goes into solution as the sodium salt. Another D-glucosaminuronic acid synthesis consists in converting D-glucosamine in liquid ammonia to 1-amino-D-glucosamine. This was isolated as the N,N-biscarbobenzoxy-1-amino-D-glucosamine and was oxidized at 90° with Adams catalyst to the uronic acid.



In a similar manner, D-galactosaminuronic acid was prepared from benzyl-N-carbobenzoxy- $\alpha$ -D-galactosamine in 76% yield (pH 7.2; 12 hours; 60°) (34). *p*-Tolyl-D-isoglucosamine can be oxidized in ammoniacal solution in the presence of platinum to D-arabonic acid. The product is isolated as the pure ammonium salt in 53% yield (35). The amadori products of *p*-anisyl- and *p*-phenethyl-D-isoglucosamine also cleave upon oxidation to give D-arabonic acid. The series of reactions [aldose  $\rightarrow$  N-glucoside  $\rightarrow$  aryl-isoaldosamine  $\rightarrow$  next lower aldonic acid] is illustrated below.



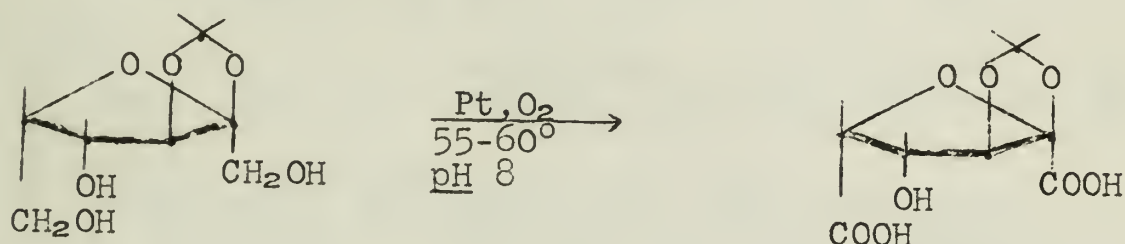




## KETOSES

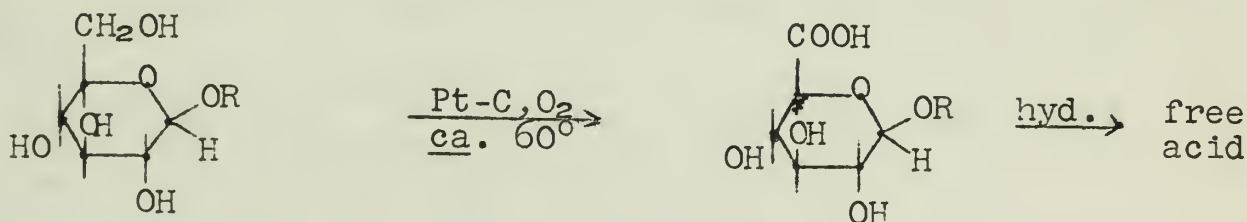
The primary hydroxyl group on C<sub>1</sub> in ketoses is very easily oxidized catalytically, giving the corresponding keto-acids. Thus, Heyns obtained 2-keto-L-gulonic acid (60% yield) from L-sorbose by catalytic oxidation with platinum on carbon at 30° (26,27). Of 30 metals tried, only platinum, palladium, and osmium operated as catalysts for the oxidation. No blocking, as was required for permanganate oxidation of diisopropylidene-sorbose, is necessary (28).

Blocking groups have been used by several workers (29,30) in the oxidation of sorbose derivatives. 2,3-4,6-Diisopropylidene-2-keto-L-gulonic acid was obtained in very good yield upon catalytic oxidation of 2,3-4,6-diisopropylidene-2-keto-L-sorbose (29). Trenner (30) prepared the dibasic acid 2,3-isopropylidene-2,5-furanose-L-gulosaccharic acid by catalytic oxidation of the L-sorbose derivative during 50 hours.



## GLUCOSIDES

D-Glucuronic acid, which is of current pharmacological interest, has been prepared by starting with a variety of glucosides as shown below.



where R =

|   |                                   |                           |
|---|-----------------------------------|---------------------------|
| $\alpha$ -CH <sub>3</sub> (36,37,38)              | $\alpha$ (-)-CH <sub>3</sub> (40) | $\beta$ -phenyl (41)      |
| $\beta$ -CH <sub>3</sub> (37)                     | $\alpha$ (-)-CH <sub>3</sub> (40) | $\beta$ -2-naphthyl (42)  |
| $\alpha$ -CH <sub>2</sub> CH <sub>3</sub> (39,38) | $\alpha$ -phosphate (37,40)       | $\alpha$ -fructose (8)    |
| $\beta$ -CH <sub>2</sub> CH <sub>3</sub> (39,38)  | $\beta$ -phosphate (40)           | $\alpha$ -saccharose (38) |

Generally, the yields are good in the oxidation step (glucoside to glucuronate); for example, sodium  $\alpha$ -methyl-D-glucuronate was obtained in 87% yield. However, strong hydrolysis is needed to obtain the free acid (glucuronate to glucuronic acid), which results in poor yields. Hydrolysis of sodium  $\alpha$ -methyl-D-glucuronate with 90% formic acid gives D-glucuronic acid in only 19% yield (37). The over-all yield (glucoside to glucuronic acid) is 16%.

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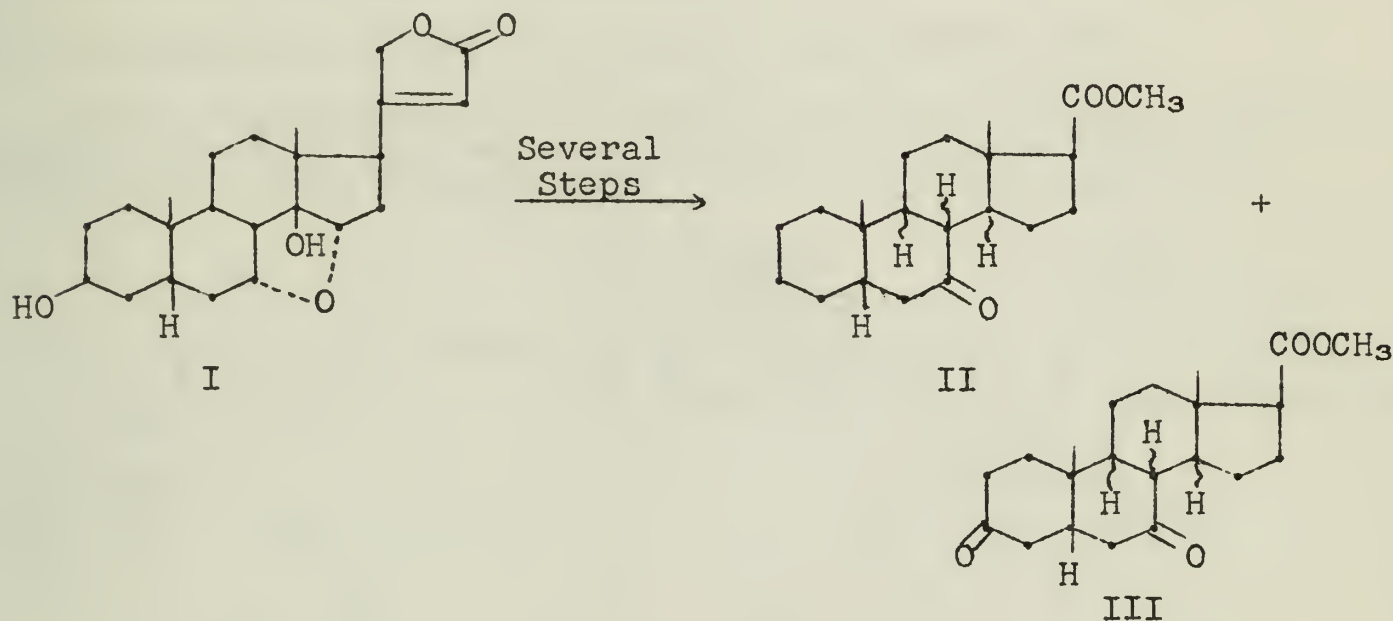
# RECENT STEROID WORK OF REICHSTEIN

Reported by J. R. Beck

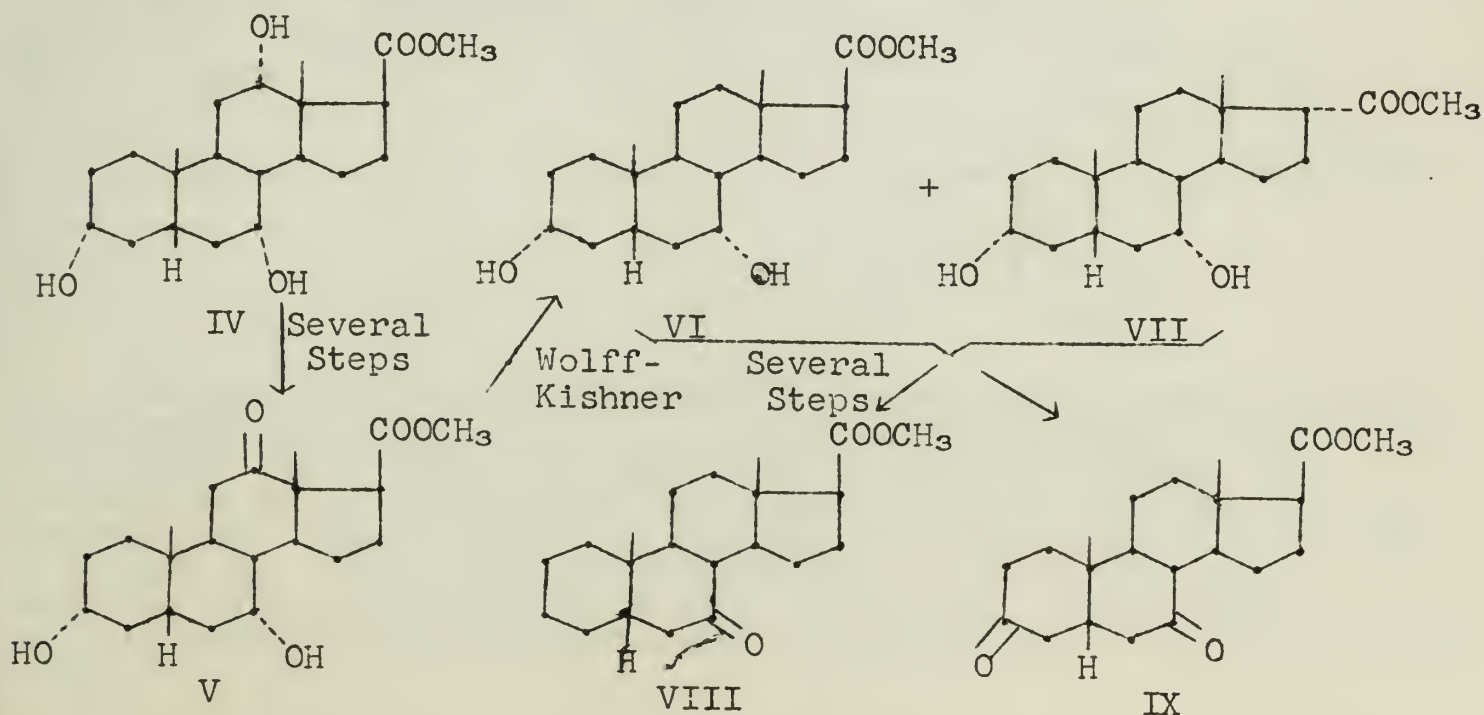
December 15, 1958

## I. INTRODUCTION

Tanghinigenin probably possesses the formula I although the exact position of the oxygen ring has not yet been established (1). Two 5 $\beta$ -androstande-17 $\beta$ -carboxylic acid methyl esters, to which the hypothetical formulae II and III have been assigned, were obtained upon degradation of tanghinigenin.



These two keto esters were different from two isomeric keto esters prepared by Lardon (2) from 3 $\alpha$ , 7 $\alpha$ , 12 $\alpha$ -trihydroxy-5 $\beta$ -androstande-17 $\beta$ -carboxylic acid methyl ester IV by way of the keto ester V. The formulae VIII and IX were assigned to these two compounds by Lardon.





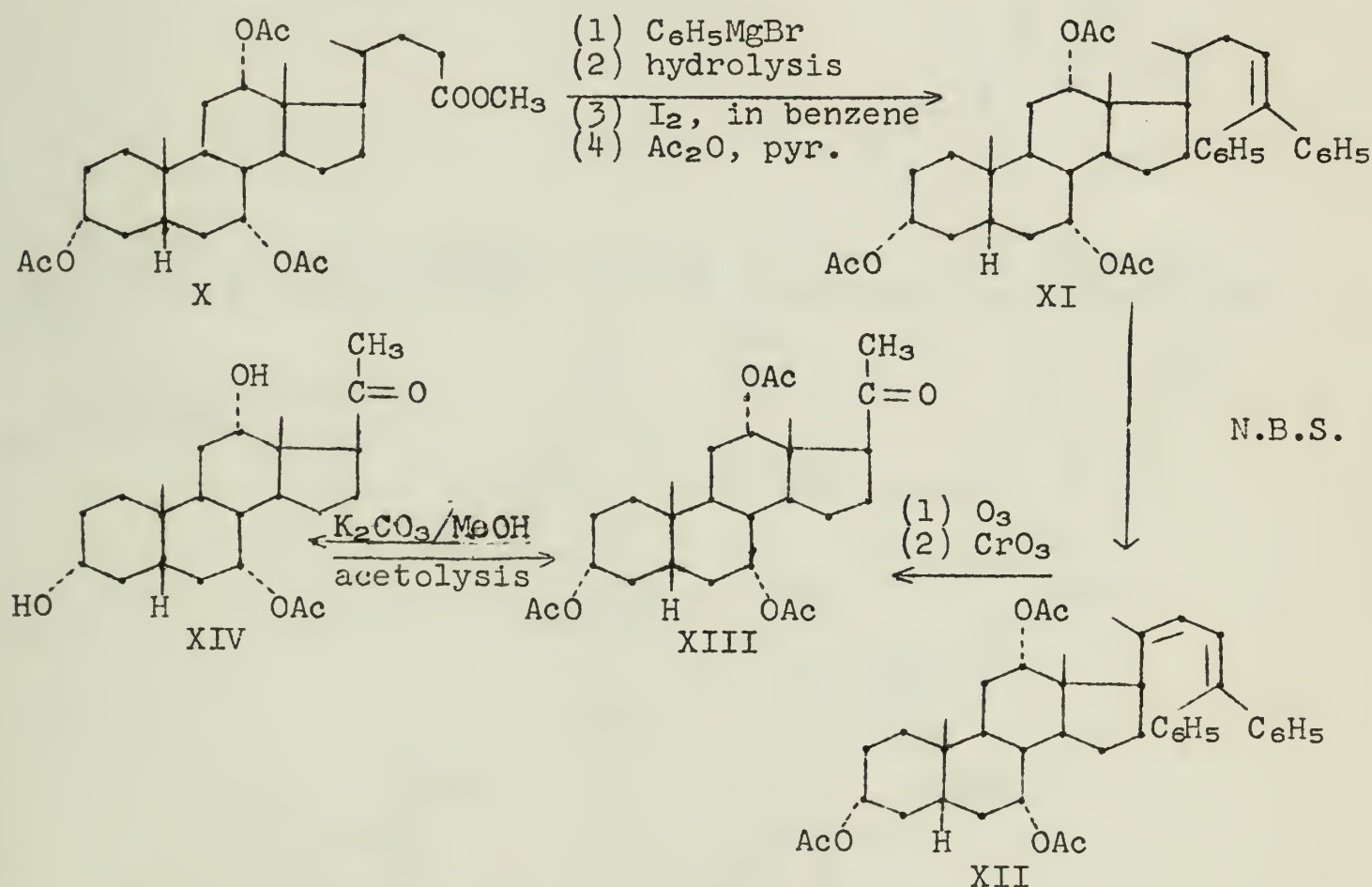


Sigg and Reichstein (3) later showed that reduction of the keto ester V under Hauptmann-Mozingo (4,5) conditions yielded the dihydroxy ester VI as the only product. However, with Wolff-Kishner reduction an additional isomeric ester was formed, to which formula VII was assigned. An analogous isomerization at C-17 had already been observed by von Euw and Reichstein (6) in the case of Wolff-Kishner reduction of androstane-17 $\beta$ -carboxylic acids.

The two esters (VI and VII) form a mixed crystallize so that it is possible that the two keto esters (VIII and IX) isolated by Lardon actually were the analogous 17 $\alpha$ -carboxylic acid methyl esters. As a result of this, Reichstein and his coworkers resynthesized these two keto esters by way of V in order to compare them with the tanghinigenin and Lardon compounds.

## II. DEGRADATION OF CHOLIC ACID UP TO THE PREGNANE STEP

Since the degradation of cholic acid by the method of Barbier and Wieland (8,9) had been shown to give low yields (10), the method of Meystre, Miescher, and Wettstein (11,12) was used.



The crystalline diphenylcarbinol resulting from treatment of X with phenyl magnesium bromide was dehydrated according to the method of Hibbert (13). After treatment with N-bromosuccinimide and subsequent dehydrobromination the resulting amorphous diene XII was treated with ozone. Oxidative cleavage of the ozonide mixture with  $\text{CrO}_3$  gave the triacetoxo ketone XIII which was isolated after reaction with Girard P Reagent (14). The final product was isolated as the dihydroxy compound XIV since it was easier to crystallize than XIII.

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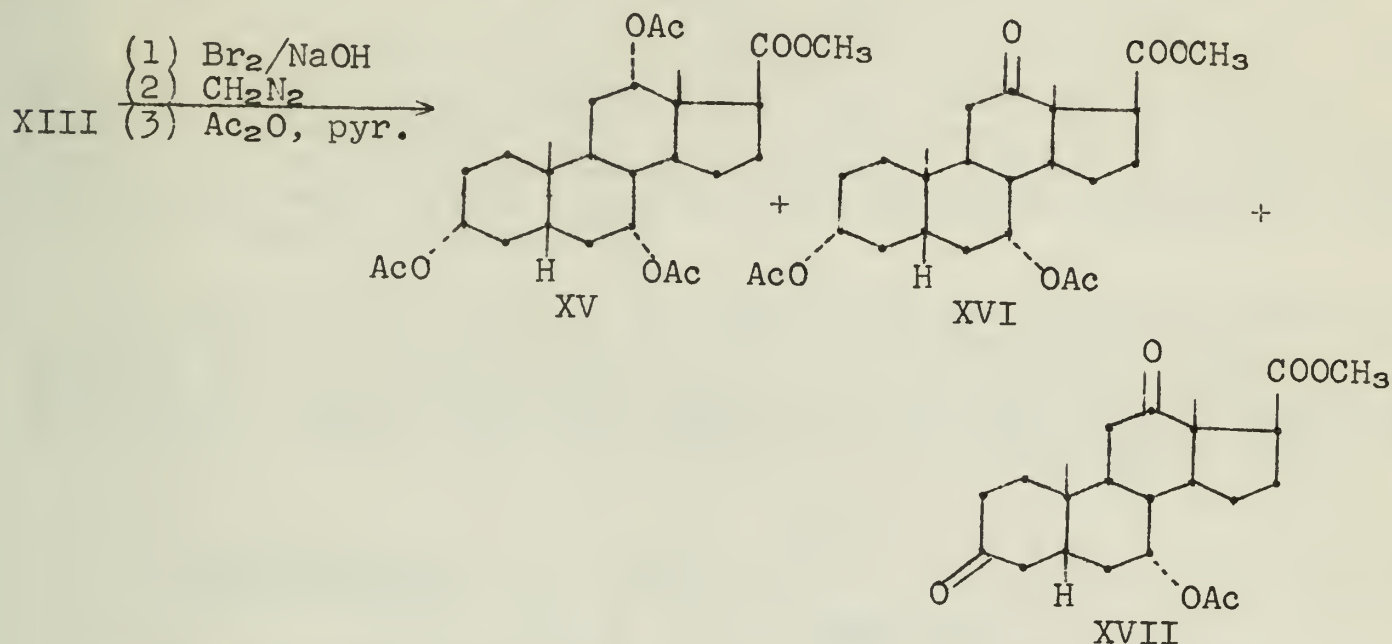
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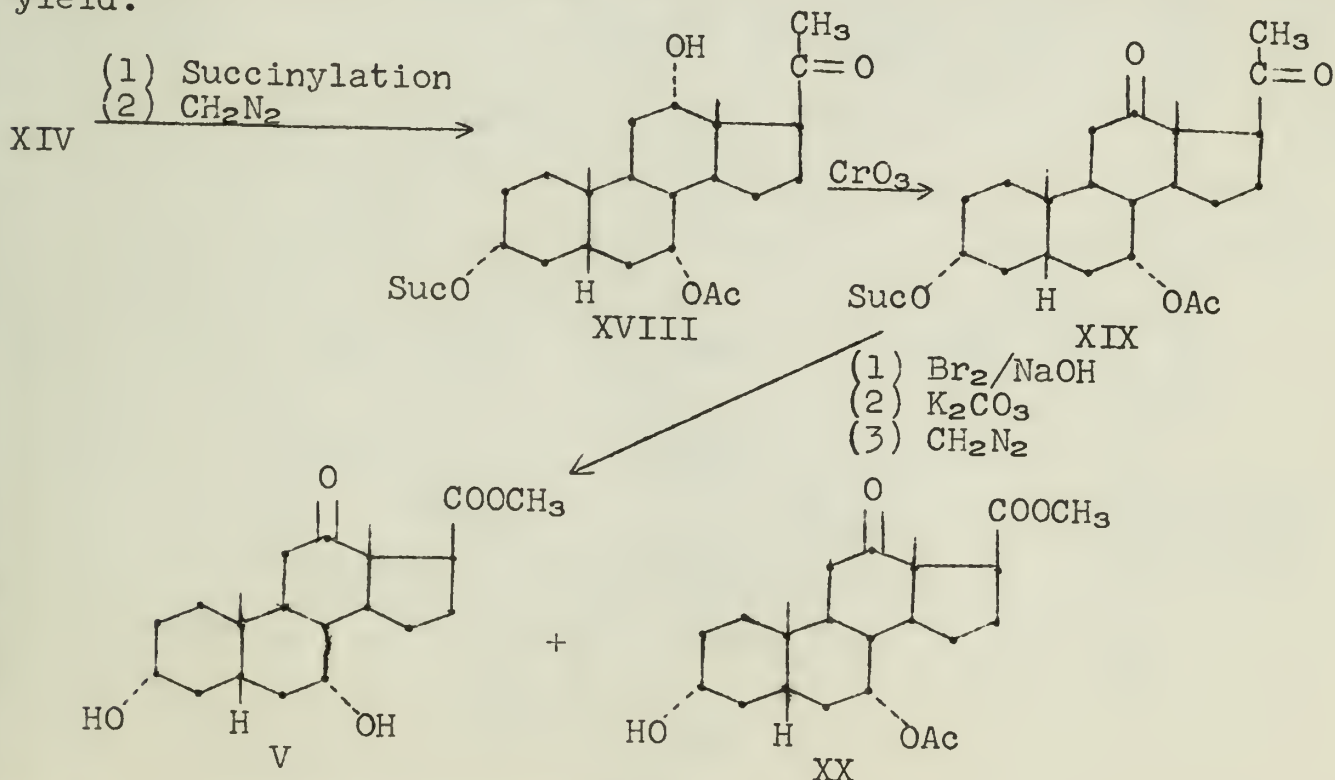
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### III. DEGRADATION UP TO THE ANDROSTANE-17 $\beta$ -CARBOXYLIC ACID STEP

The degradation of 3 $\alpha$ , 7 $\alpha$ , 12 $\alpha$ -triacetoxy-20-keto-5 $\beta$ -pregnane XIII to the androstane-17 $\beta$ -carboxylic acid step was accomplished by means of the haloform reaction. Under the same conditions used by Casanova and Shoppee (15), about 40-60% yield of acidic component was obtained. Methylation followed by acetylation and chromatography gave the three esters XV, XVI, and XVII.



However, a more convenient route to V was found involving hypohalite oxidation of XIX. The two esters were obtained in 62% yield.



### IV. SYNTHESIS OF THE DESIRED KETO ESTERS

For the preparation of VI, the keto ester V was treated with o-xylene dimercaptan (16,17,18). The resulting compound XXII, obtained in 50% yield, was desulfurated with Raney Ni (4). Succinylation followed by methylation and CrO<sub>3</sub> oxidation yielded the

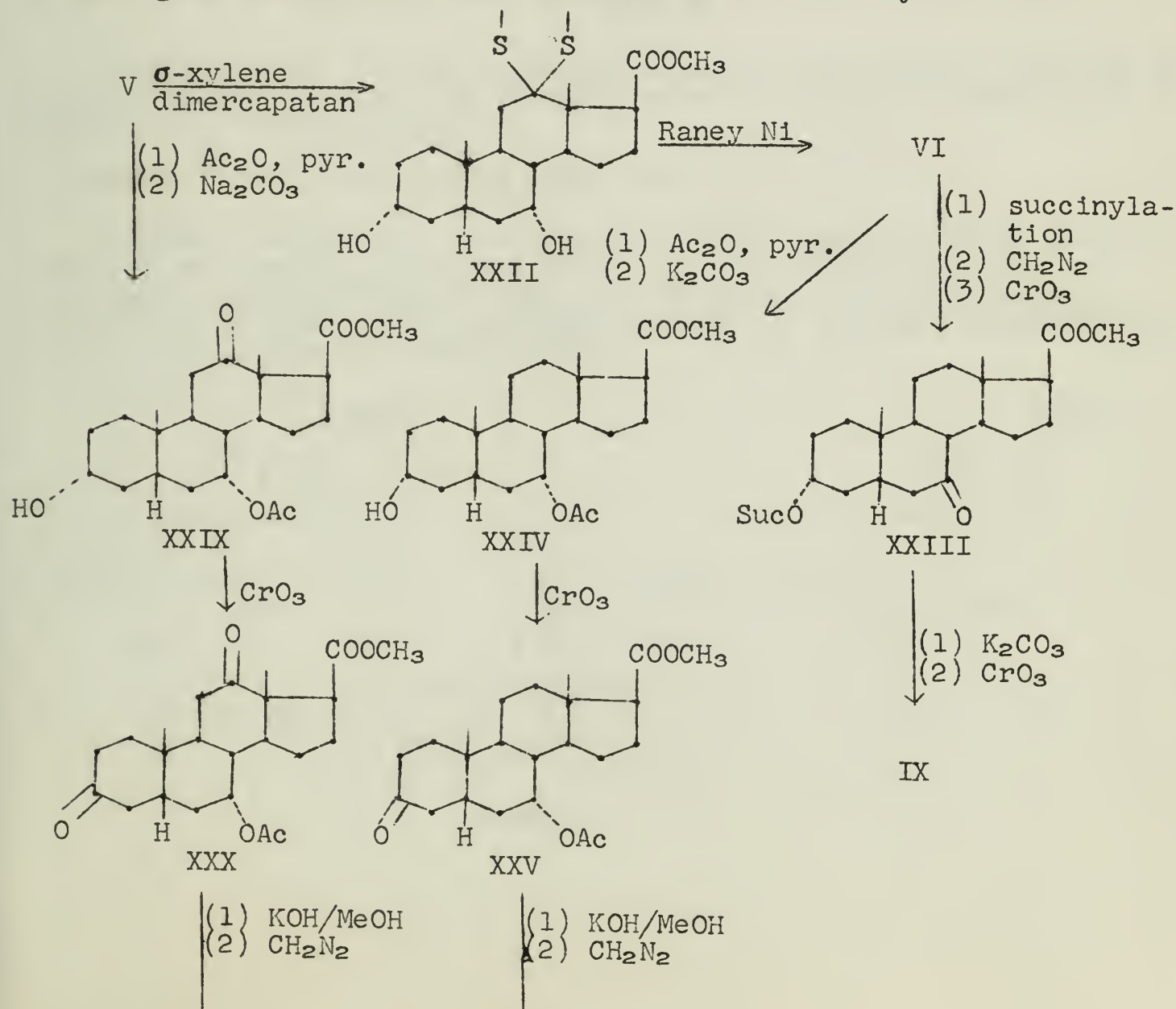




crystalline ester XXIII, which was identical with Lardon's preparation. From this it followed that in the original preparation of XXIII by Lardon from the mixed crystallizate (VI and VII), the derivative formed from VII was left behind in the supernatant after crystallization of XXIII. The diketo ester IX was obtained from XXIII by saponification and  $\text{CrO}_3$  oxidation.

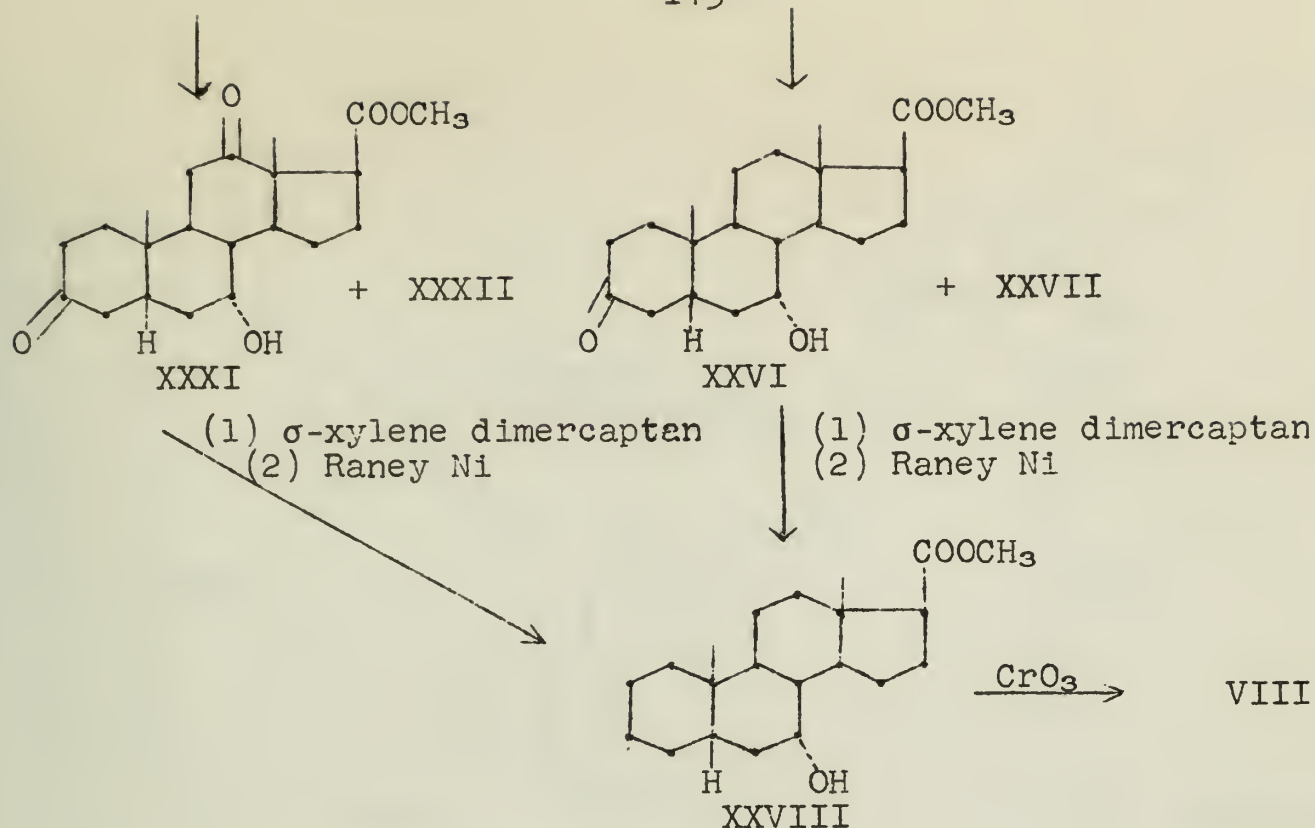
The keto ester VIII was prepared in two different ways. Acetylation of V followed by partial saponification yielded XXIX which was oxidized to give the diketo acetoxy ester XXX. Saponification of XXX followed by methylation gave an unexpected result. In addition to the diketo hydroxy ester XXXI, an isomeric compound XXXII was formed (in the ratio 3:1). The nature of this unexpected isomer will be treated in the next section. Reduction of XXXI gave the hydroxy ester XXVIII (identical with Lardon's preparation) which was then oxidized to give VIII.

In the second method VI was acetylated and partially saponified to give XXIV. Oxidation yielded the keto acetoxy ester XXV. Alkaline saponification again gave the expected keto hydroxy ester XXVI plus an unexpected isomer XXVII (in the ratio 3:1). Reduction of XXVI gave XXVIII which was oxidized as before to yield VIII.





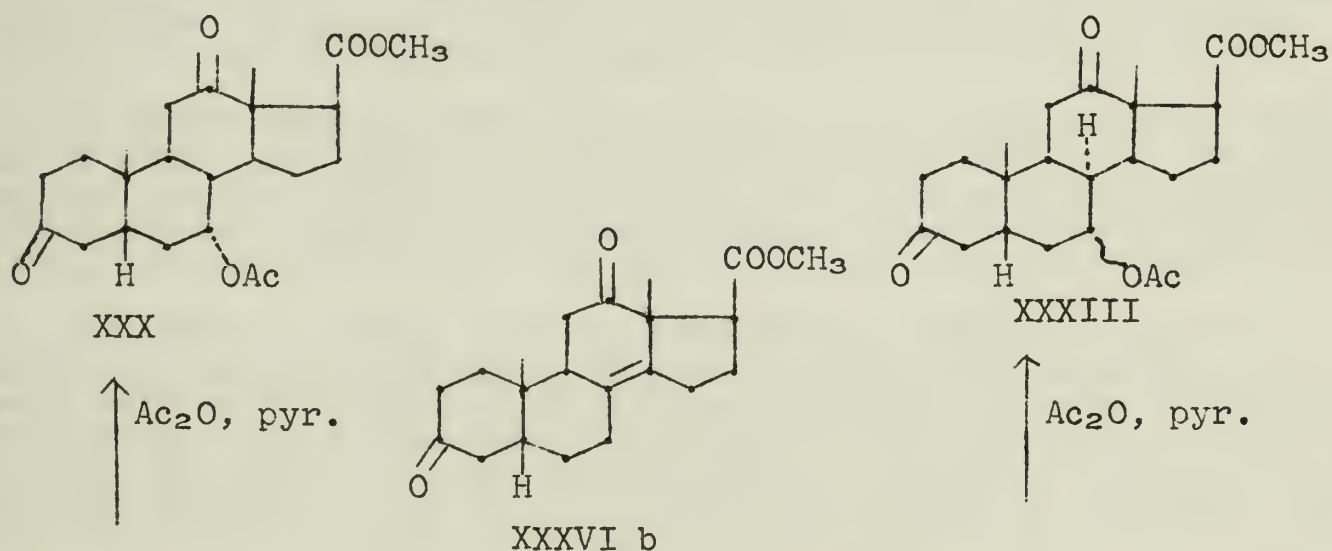




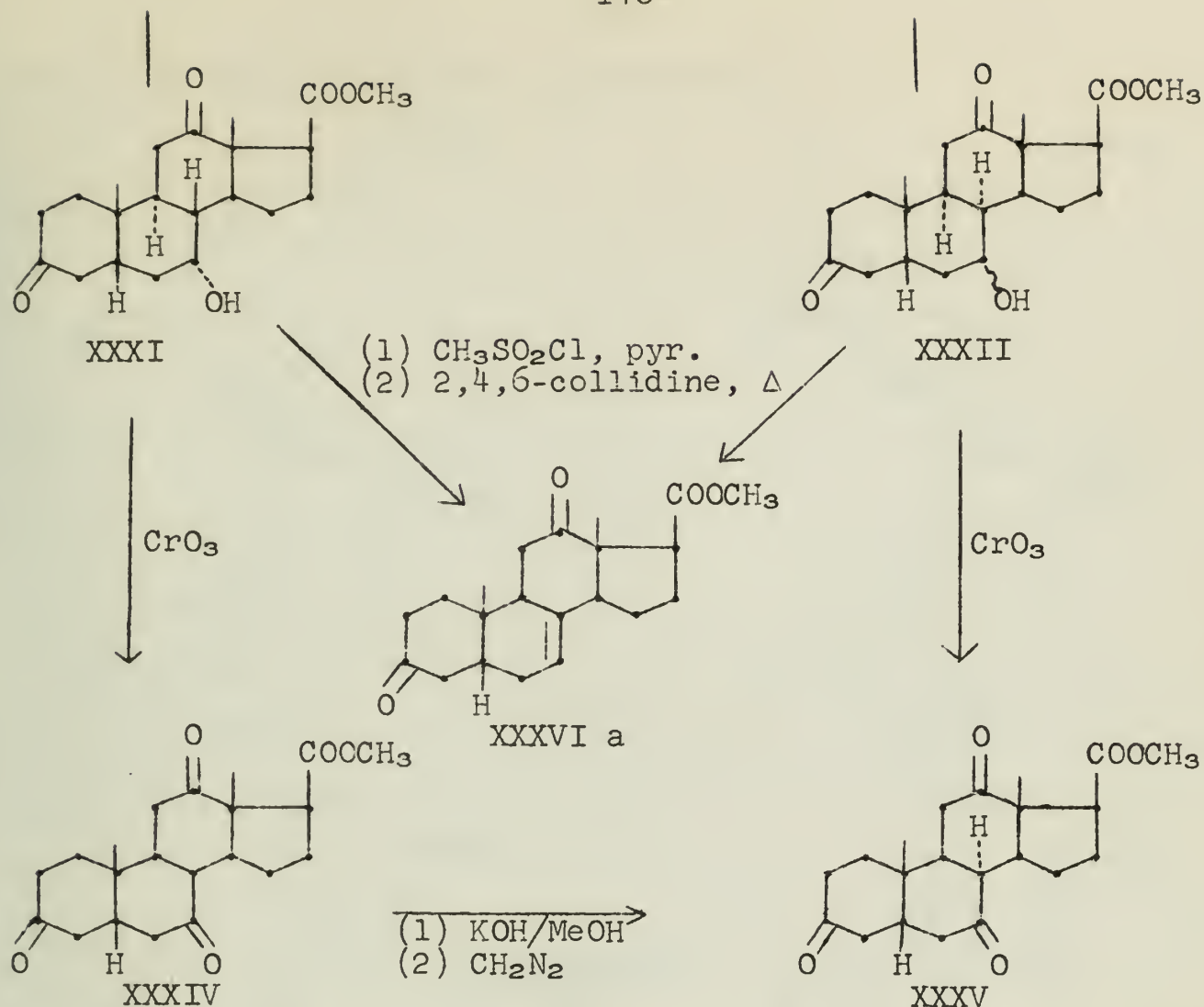
From this work it was concluded that the keto esters VIII and IX were not identical with the two keto esters II and III obtained by degradation of tanghinigenin.

#### V. NATURE OF THE KETO ESTERS XXXII AND XXVII

Jungmann, Schindler, and Reichstein (19) have presented evidence that the keto esters XXXII and XXVII probably differ from their respective isomers XXXI and XXVI only by means of isomerization at C-8 and C-7 (although the configuration at C-7 in XXXII and XXVII has not been conclusively established).







Acetylation of XXXI yielded the starting material XXX, whereas acetylation of XXXII gave a crystalline acetoxy derivative which could not be identified with any known steroid. Oxidation of XXXI gave the known triketo ester XXXIV, while oxidation of XXXII gave an unknown triketo ester XXXV. From this it was evident that the difference between XXXI and XXXII was not due to isomerization at C-7 alone.

An isomerization at C-17 was unlikely since the specific rotation of XXXII was about 30° higher than that of XXXI. If isomerization had occurred only at C-17 a lowering of the specific rotation to a value between -60 and -90° would have resulted. That isomerization at C-17 had not taken place was also shown by chemical methods.

Treatment of either XXXI or XXXII with CH<sub>3</sub>SO<sub>2</sub>Cl in pyridine followed by heating with 2,4,6-collidine (20) gave the same unsaturated diketo ester XXXVI a. The infrared spectrum of XXXVI a showed only a small shoulder at 3000 cm.<sup>-1</sup> and only a weak band in the area 805-810 cm.<sup>-1</sup>, which would indicate that the double bond had probably migrated to the 9-11 position as in XXXVI b. However, the exact position of the double bond was not significant in this case.

From the above chemical evidence it appeared that compounds XXXI and XXVII could only be different at C-7, C-8, C-9, and/or C-14. That the real isomerization had occurred at C-8 and not C-9 or C-14 was shown by heating XXXIV with methanolic KOH. After methylation a mixture of esters XXXIV and XXXV was formed. The mixture was separated by preparative paper chromatography and the two esters were identified by comparison with samples of XXXIV and XXXV obtained by



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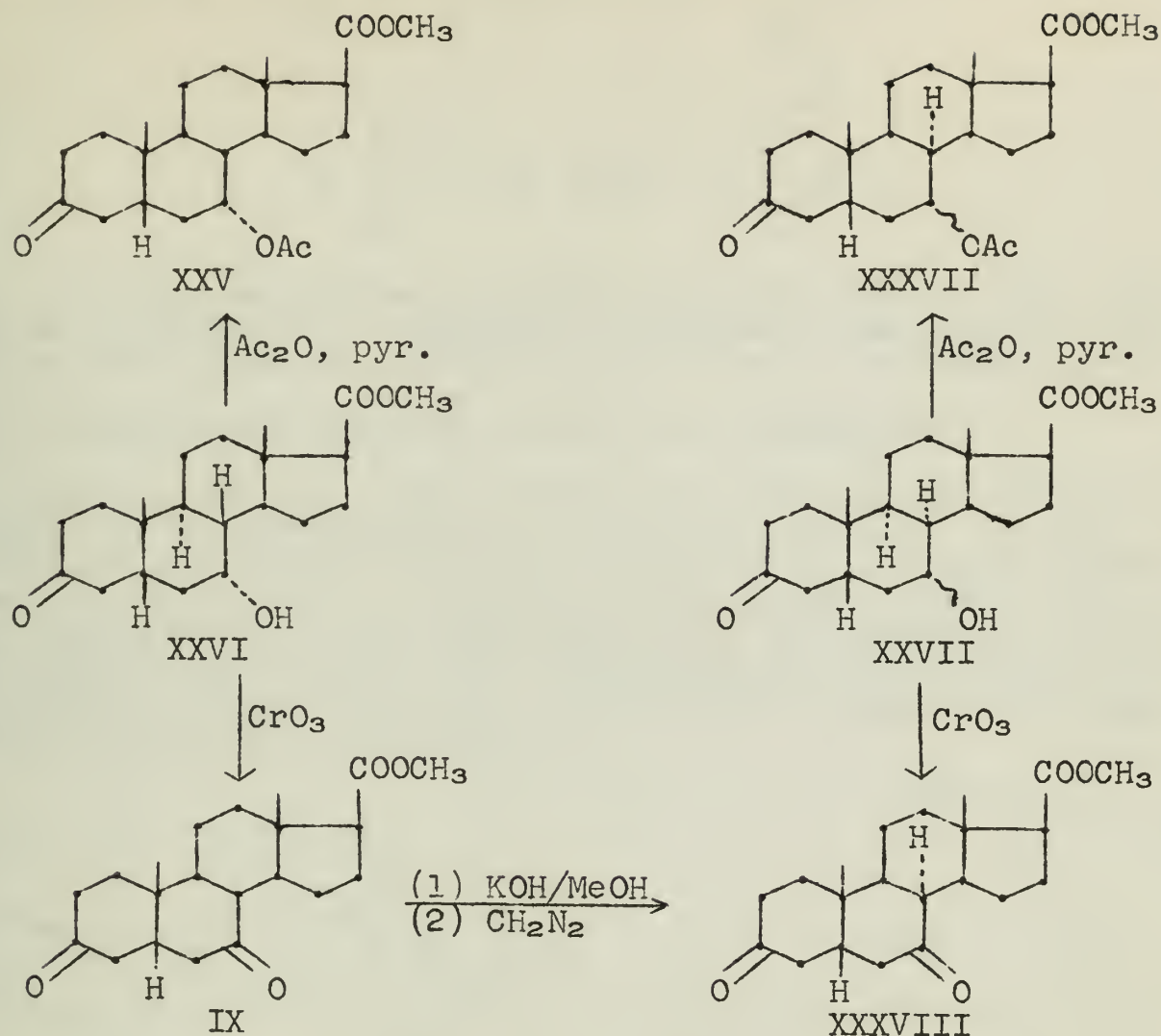
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$$\frac{d}{dt} \left( \frac{\partial L}{\partial \dot{x}} \right) = \frac{\partial L}{\partial x}$$

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oxidation of XXXI and XXXII, respectively.



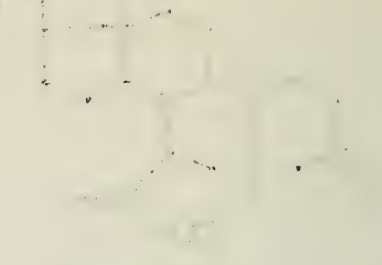
Similarly, in the case of the isomeric esters XXVI and XXVII it was shown that XXVI contained the normal steroid structure since it returned XXV on acetylation and gave the known diketo ester IX on oxidation. Acetylation of XXVII gave an acetoxo derivative which could not be crystallized. Oxidation of XXVII gave a diketo ester XXXVIII which was isomeric with IX and which was different from the known 3,7-diketo-5 $\beta$ -androstane-17 $\alpha$ -carboxylic acid methyl ester. Again it was found that IX could be converted partly into XXXVIII by heating with methanolic potassium hydroxide.

Under the conditions used, an equilibrium probably exists between IX and XXXVIII as well as between XXXIV and XXXV. The fact that the 8 $\alpha$  derivatives are present in considerable amounts (20-25%) shows that in the case of the 7-keto-5 $\beta$ -steroids, only a slight energy difference must exist between the 8 $\alpha$  and 8 $\beta$  epimers.

In the case of the unexpected isomerization of XXXI to XXXII and of XXVI to XXVII, the assumption might be made that the process is occurring by way of a common enolate ion by means of a reduction-oxidation process.

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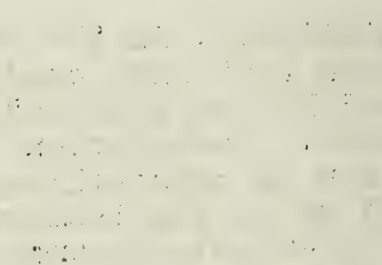
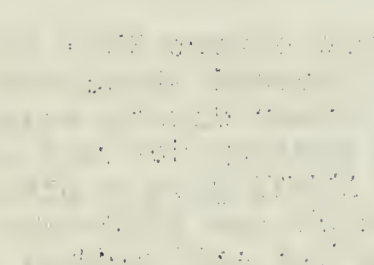
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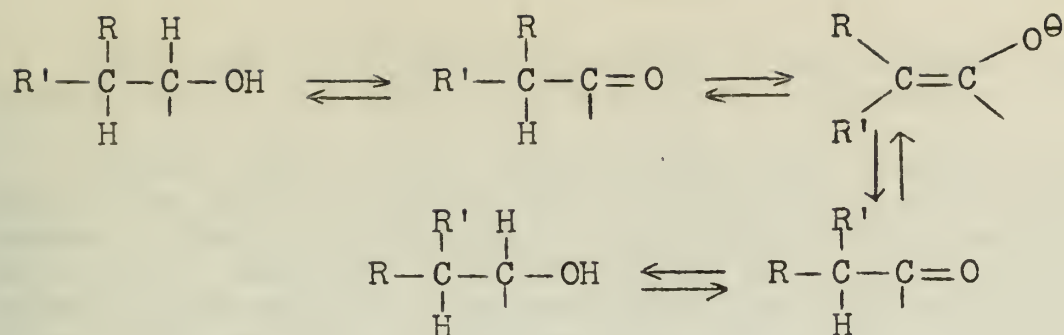


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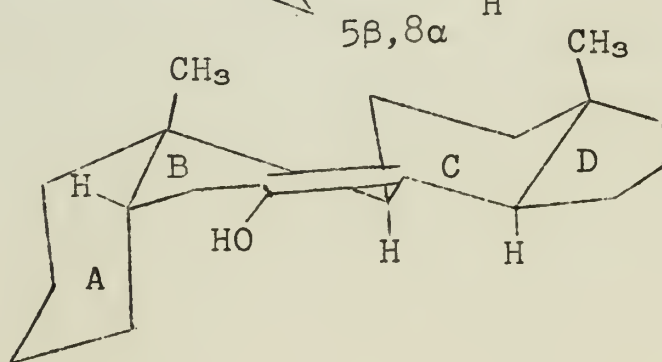
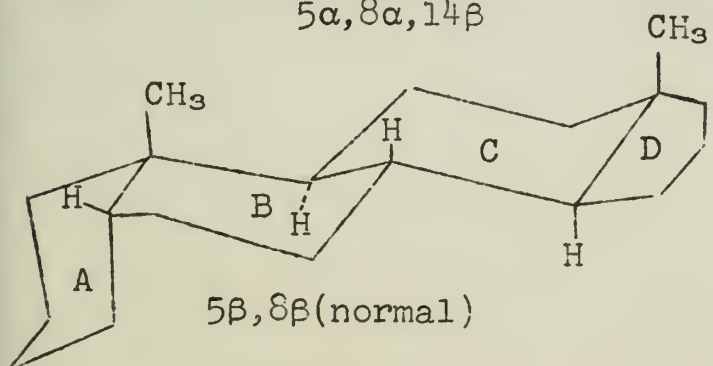
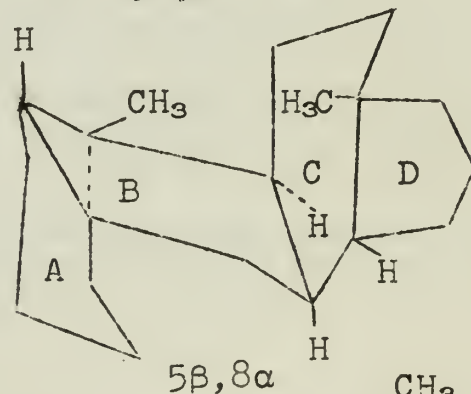
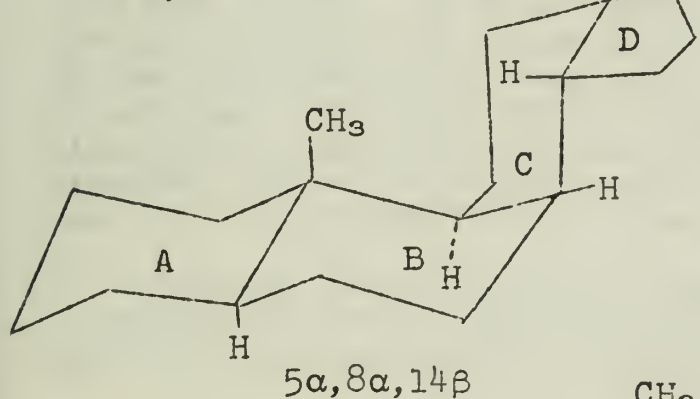
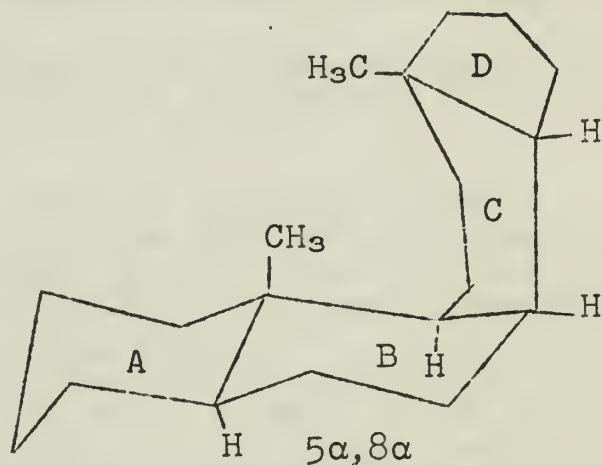
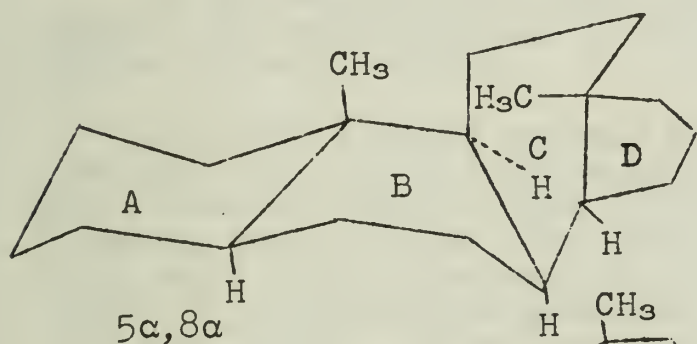




A similar mechanism has been assumed to explain the isomerization of alcohols (21), although considerably more drastic conditions are necessary than were used in the instances reported above.

## VI. PROBABLE CONFIGURATION OF THE $5\beta$ , $8\alpha$ -STERIODS

The unusual keto esters described above are the first reported examples of  $8\alpha$ -steroids with the  $5\beta$ -configuration. In the  $5\alpha$  series as well as the series with double bonds at C-4, a large number are known (22,23,24,25,26). In the  $5\alpha$ ,  $8\alpha$ -steroids either ring B or ring C must exist in the boat form (24). Formation of an all-chair conformation would result in a trans-diaxial fusion of either the A or D rings. However,  $5\alpha$ ,  $8\alpha$ ,  $14\beta$ -steroids (rings C and D cis) can assume an all-chair conformation.

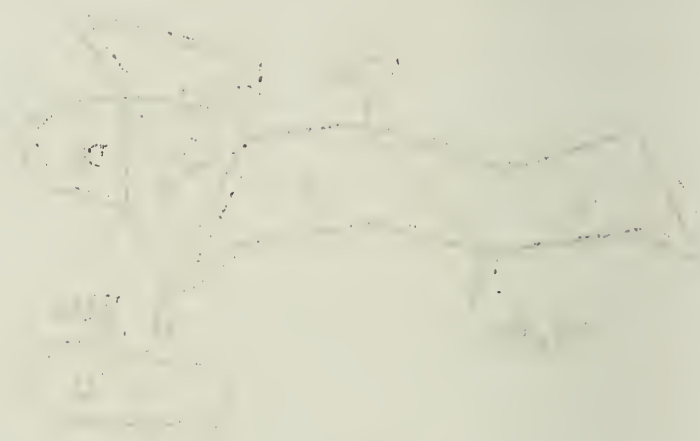
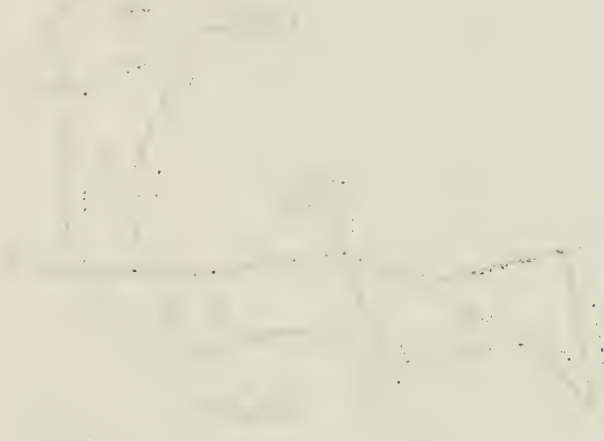


1. The first part of the report is a general description of the project and its objectives. This includes a brief history of the project and a statement of the problem being addressed. The second part of the report is a detailed description of the methodology used in the study. This includes a description of the data collection methods, the statistical methods used for data analysis, and the criteria used for selecting the sample. The third part of the report is a description of the results of the study. This includes a description of the data collected, a summary of the statistical results, and a discussion of the implications of the findings. The fourth part of the report is a conclusion and a list of references.

2. The second part of the report is a detailed description of the methodology used in the study. This includes a description of the data collection methods, the statistical methods used for data analysis, and the criteria used for selecting the sample. The third part of the report is a description of the results of the study. This includes a description of the data collected, a summary of the statistical results, and a discussion of the implications of the findings. The fourth part of the report is a conclusion and a list of references.

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With the  $5\beta,8\alpha$ -steroids (rings A and B cis) a similar situation exists and an all-chair conformation is possible.

In the case of the intermediate enol formed during the isomerization the double bond at C-7 could cause C-atoms 6,7,8,9 and 14 to assume a planar configuration whereupon ring B assumes a half-chair form (27). Addition of a proton to the  $\beta$ -position leads to the normal  $5\beta,8\beta$ -steroid, whereas addition of a proton to the  $\alpha$ -position gives first of all a conformation with ring B in the boat form. Here the possibility exists for rearrangement to the all-chair form given above ( $5\beta,8\alpha$ ) if the latter is more stable and it probably is. In the all-chair form rings A and B are arranged directly inverted from the normal  $5\beta,8\beta$ -steroids, while rings C and D remain unchanged. This means that all substituents in rings A and B which were originally arranged axial are now arranged equatorial, and vice versa. Thus, a  $3\alpha$ -hydroxyl group arranged equatorial in the normal steroid converts to an axial conformation after isomerization at C-8.

Since equatorial and axial acetoxy derivatives can be differentiated by their infrared spectra (28), it should be possible to prove the conformation of  $5\beta,8\alpha$ -steroids by isomerizing  $3\alpha$ -hydroxy-7-keto- $5\beta$ -androstane-17 $\beta$ -carboxylic acid methyl ester.

After isomerization and acetylation the infrared spectrum should exhibit the complex bands of axial acetoxy derivatives if it occurs in the all-chair form.

However, for the present the infrared spectrum has been examined only for the determination of the spatial arrangement of the 7-acetoxy group in the  $5\beta,8\alpha$ -ester XXXIII. The spectrum shows a strong band between 1230 and 1240  $\text{cm}^{-1}$  with a sharp maximum at 1230  $\text{cm}^{-1}$  and a shoulder at about 1232-1238  $\text{cm}^{-1}$ . In this same region 3,12-diketo- $5\beta$ -androstane-17 $\beta$ -carboxylic acid methyl ester does not absorb. This indicates that the 7-acetoxy group is probably axial, and if one assumes that the all-chair conformation is the preferred one, then the 7-acetoxy group is located in the  $\beta$ -position. However, if the form with ring B in the boat form is also present at room temperature, then a complex spectrum would be expected for a  $7\alpha$ -acetoxy group due to the possibility of rearrangement to a conformation in which the C-ring assumes the boat form.

Whether or not similar isomerizations occur in the case of other 7-hydroxy-steroids has not yet been investigated. Also the role of the 3-keto group, if any, is still unknown.





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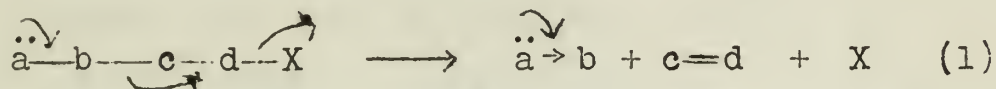


## FRAGMENTATION IN POLAR REACTIONS

Reported by D. J. Anderson

December 18, 1958

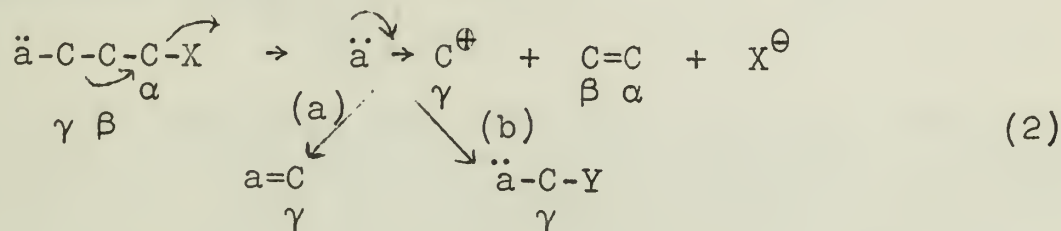
In the literature of organic chemistry there is a considerable number of apparently different types of reactions which on close examination may be shown to conform to the following general mechanism.



The symbols a to d represent a sequence of atoms that can easily form double bonds; therefore carbon, nitrogen or oxygen. The atom or group X is characterized by its ability to form an anion by accepting completely a pair of electrons from the d-X bond. The connection between d and X will not be broken if the atom d is doubly or triply bound to X. Atoms or groups which may assume the function of X are halogens, esters of strong acids such as tosylates,  $-\text{OH}_2^+$ ,  $-\text{NR}_3^+$ ,  $\text{C}=\text{NR}$ ,  $\text{C}\equiv\text{N}$ ,  $\text{C}=\text{O}$ ,  $-\text{OCrO}_2\text{H}$  (1,2,3),  $-\text{Pb}(\text{OAc})_3$  (4,5).

The mechanism is characterized by the fact that the bond between d and X and that between b and c are cleaved heterolitically. The atom or group X becomes negatively charged and b becomes correspondingly positively charged. A double bond is formed at least temporarily between c and d. Further, it is essential that the positive charge arising at b can be stabilized through electron donation by a. This may be done through induction or hyperconjugation (horizontal arrow) or through coordination of an electron pair (curved arrow). In the latter case a double bond would be formed between a and b. Groups which can assume the function of a are therefore alkyl, aryl, -OH, -OR, -NH<sub>2</sub>, -NR<sub>2</sub> as well as actual or potential carbanions.

The reactions to be considered are those in which the symbols b, c and d of scheme (1) represent carbon atoms. Thus the less general scheme (2) may be written.



a = alkyl, aryl,  $\begin{array}{c} \cdot \\ \cdot \\ \text{C} \\ \cdot \\ \cdot \end{array}$ , HO-, RO-, NH<sub>2</sub>-, NR<sub>2</sub>-.

X = halogen,  $\text{OH}_2^+$ ,  $-\text{OTs}$ ,  $-\text{NR}_3^+$ .

The positive charge arising at  $C_\gamma$  through fragmentation can now react in two ways. Either coordination of an electron pair from  $a$  occurs with formation of a double bond between  $a$  and  $C_\gamma$  (process a) or coordination of a nucleophilic species  $Y$  present in the medium (process b). The first process corresponds to an elimination, the second to a substitution.

There are numerous reactions in which the atom a of scheme (2) is oxygen. Examples are the cleavage of anions of certain  $\beta$ -haloacids

THE UNIVERSITY OF CHICAGO

CHICAGO, ILL. 60637

TO THE PRESIDENT OF THE UNIVERSITY OF CHICAGO  
FROM THE DEAN OF THE FACULTY

Dear Sir:

I have the honor to acknowledge the receipt of your letter of the 15th inst. regarding the proposed changes in the curriculum of the Faculty of Divinity. The Faculty of Divinity has been studying this matter for some time and has reached a preliminary conclusion that the proposed changes are desirable. I am sure that you will be pleased to hear of this result.

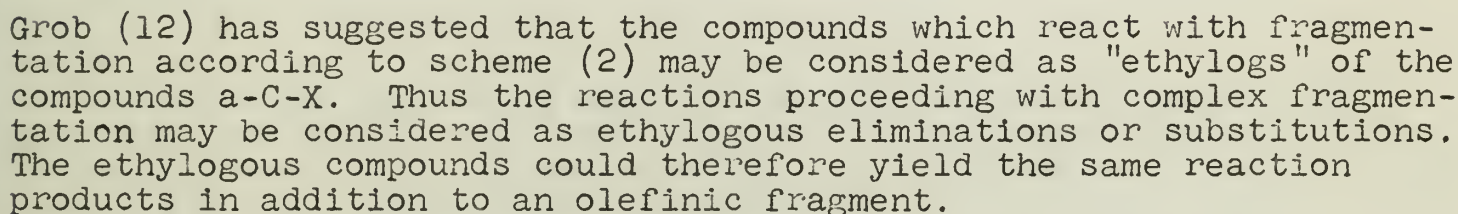
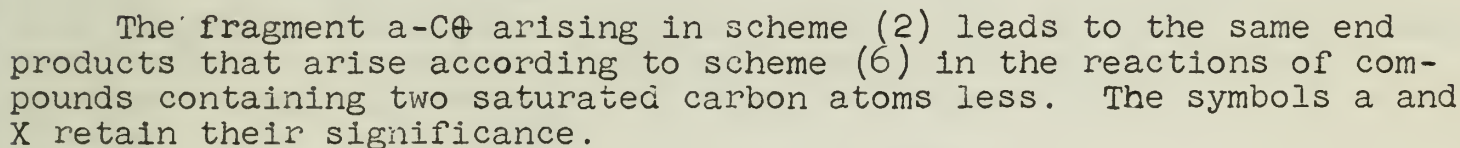
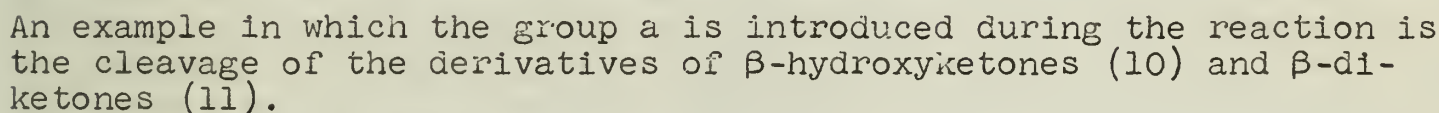
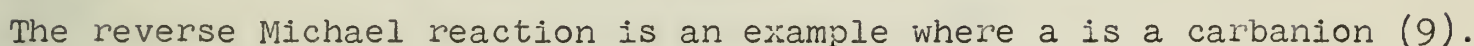
The Faculty of Divinity has also decided to recommend that the proposed changes be implemented as soon as possible. I am sure that you will be pleased to hear of this result. The Faculty of Divinity has also decided to recommend that the proposed changes be implemented as soon as possible. I am sure that you will be pleased to hear of this result.

I am, Sir, very respectfully,  
Your obedient servant,  
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Very truly yours,  
[Signature]

Very truly yours,  
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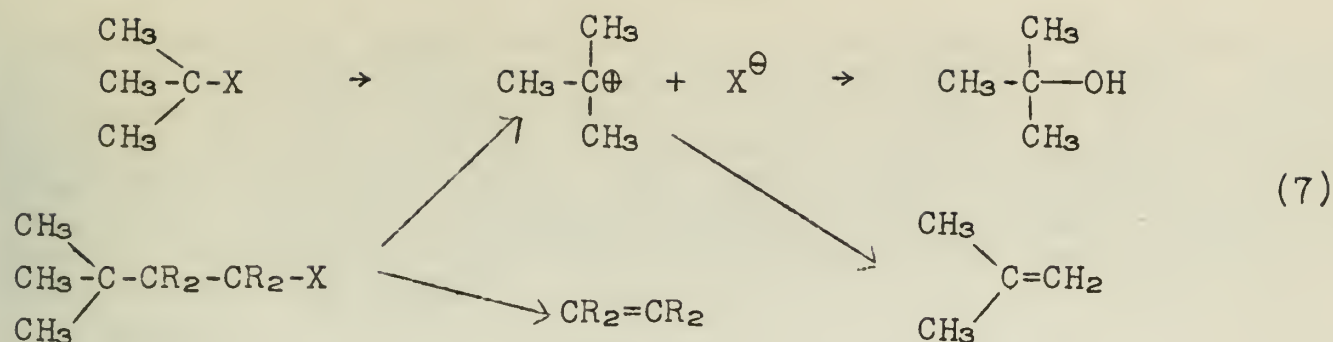
Very truly yours,  
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Scheme (7) combines the known reactions of  $\alpha$ -branched alkyl halides and alcohols with the fragmentation reactions of the corresponding ethylogs (5,13,14). Fragmentation predominates when  $C_\beta$  is substituted, probably because then the 1,2-elimination of HX is suppressed and fragmentation allows a relief of steric strain in the molecule.

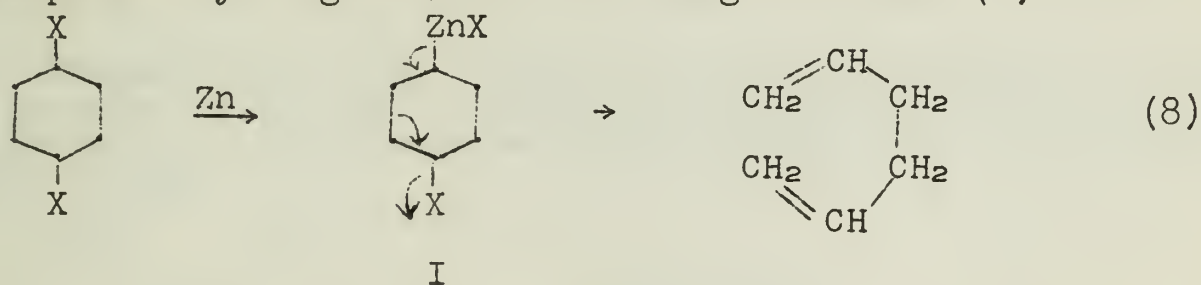






The concept of ethylogy in organic chemistry led Grob to investigate the reactions of saturated 1,4-dihalides with zinc (15). The known 1,2-elimination of halogen from ethylene bromide when treated with zinc may be compared with the reaction of its ethylog, 1,4-dibromobutane under the same conditions. The early literature reports that this latter reaction gives rise to ethylene (17). However, later workers were unable to detect any ethylene in the reaction of the 1,4-dihalide with magnesium in dibutyl ether (16). The 1,4-dibromocyclohexanes have been shown to react with sodium in isoamyl ether to give small amounts of bialllyl. The first report of this reaction (18) mentions a hydrocarbon fraction, assumed to be bicyclo[2.2.0]hexane. It was shown later that the fraction actually consisted of a mixture of simple hydrocarbons (19).

Grob (15) repeated the reaction using pure crystallized cis- and trans-1,4-dibromo and diiodocyclohexanes and obtained 8% bialllyl accompanied by larger amounts of benzene, cyclohexene and small amounts of 2,4-hexadiene and 1,3-cyclohexadiene. The reaction of the cis-1,4-dibromocyclohexane with zinc dust in dioxane produced almost 70% bialllyl. The trans-isomer gave similar results. In the case of the iodo compounds the product comprised almost 90% bialllyl. Under these conditions the reaction may be formulated as a 1,4-elimination accompanied by fragmentation according to scheme (8).



It is remarkable that there is no difference in the rate of formation of bialllyl from the isomeric 1,4-dihalocyclohexanes. This fact appears to be in contrast to the 1,2-elimination of halogen with iodide ion which shows high stereochemical selectivity (20,21). Grob offers the explanation that both isomeric halides yield the same organo-zinc compound I and that this compound has the most stable configuration (presumably the ZnBr-C bond is equatorial). This assumption is based on the fact that lithium and sodium organic compounds are configuratively unstable (22,23). The suggestion is made that this holds true for zinc and magnesium organic compounds in spite of extensive covalent character of the metal-carbon bond.

The analogous reaction of zinc with 1,4-dibromobutane was shown to give rise to ethylene only very slowly (10% ethylene after 20 hrs.). Grob suggests that the reaction may be considered as two trans-eliminations coupled with one another and that the most stable form,

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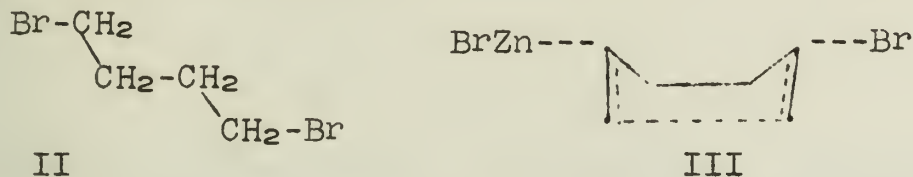
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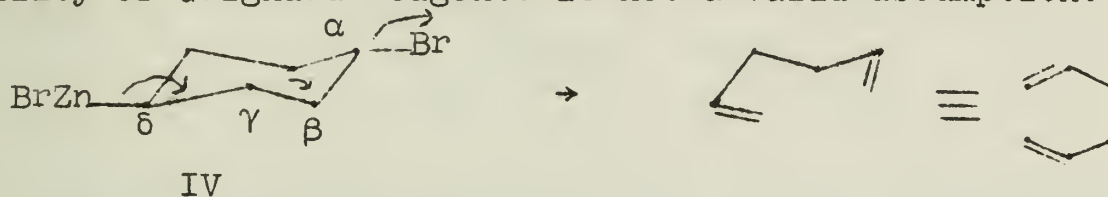
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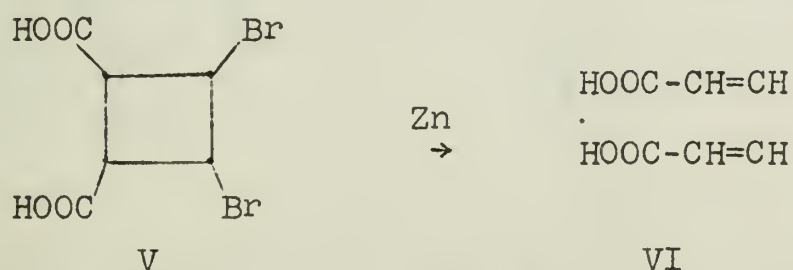
namely the planar trans-configuration II of the 1,4-dihalide is the conformation exhibiting the required stereochemistry (24). Further, he states that for fragmentation to occur in the 1,4-dihalocyclohexanes, the 1,4-substituents and the four intervening carbon atoms should be in the same plane. This would lead to transition state III. The common organozinc compound proposed by Grob would be expected to exist in the boat form in appreciable amounts at the temperature of the reaction (100°) (25).



A more careful examination of the steric requirements for elimination reveals that in the transition state the developing p-orbitals must overlap. Thus the two bonds being broken in a 1,2-elimination should be parallel or at least coplanar. This does not imply that the two leaving groups in a 1,4-elimination should be coplanar with the four intervening carbon atoms. For a 1,4-elimination with fragmentation to occur in the trans-1,4-dihalocyclohexanes, overlap of the developing p-orbitals can occur when the organo-zinc compound IV is in the chair form. Thus the only steric requirements for 1,4-elimination are that the C<sub>α</sub>-Br and the C<sub>δ</sub>-ZnBr bonds be parallel to the C<sub>β</sub>-C<sub>γ</sub> bond. Thus, 1,4-elimination with fragmentation may occur when the six atoms concerned lie in one or two planes which intersect in the central C-C bond. Therefore, Grob's argument concerning the configurational stability of Grignard reagents is not a valid assumption.



Fragmentation with elimination has been observed in a dibromocyclobutane system (26). Thus, the reaction of zinc on 1,2-dibromocyclobutane-3,4-dicarboxylic acid (V) yields the 1,3-butadiene derivative VI (26).

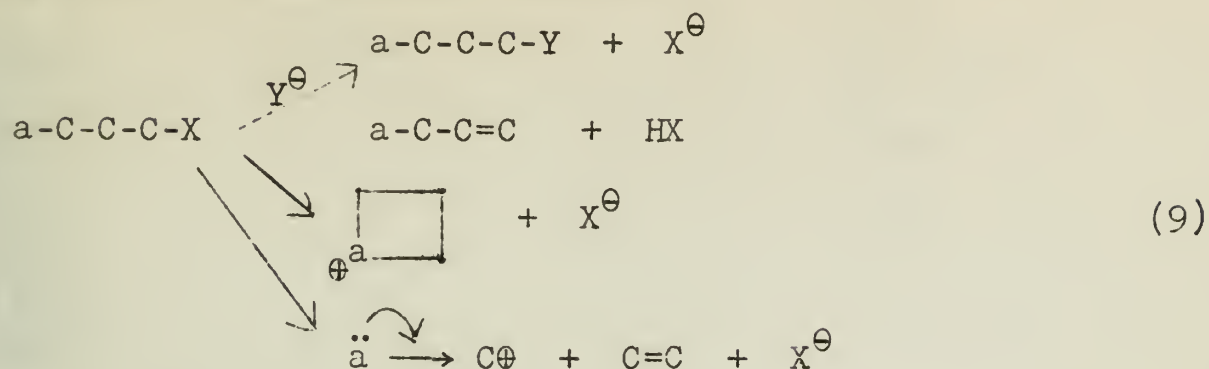


Grob suggested that in this reaction the 1,4-elimination predominated over the customary 1,2-elimination. However, a recent paper reports that at 75° the reaction gives the expected cyclobutene derivative which rapidly isomerises at 120° to the butadiene derivative VI (27).

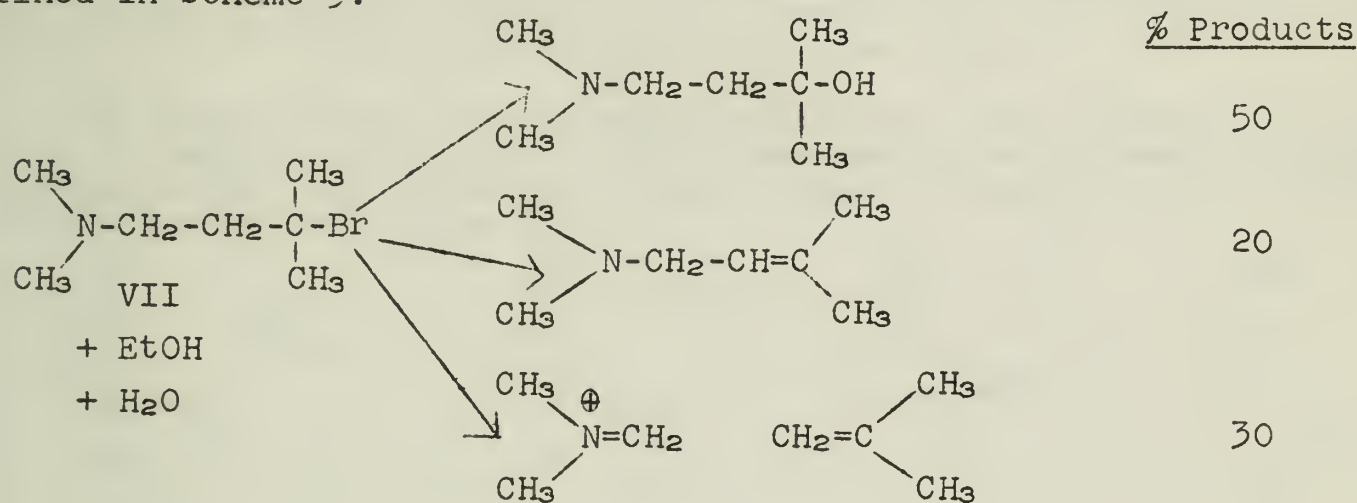
The question arises whether 1,4-elimination with fragmentation occurs via a stepwise or a concerted process. If a stepwise mechanism predominates then there are several possibilities for the course of the reaction. The intermediate carbonium ion could react with a nucleophile, lose a proton to form an olefin, undergo ring closure or



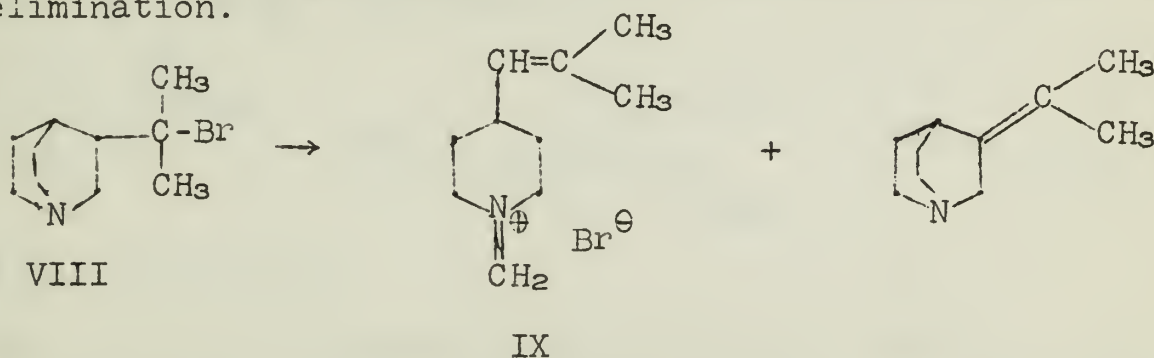
give rise to fragmentation products.



The relative proportions of the possible reactions will depend on the reaction conditions, the degree of substitution of the chain and on the spatial arrangement of the chain. The solvolysis of the following  $\gamma$ -bromoamine VII (12) illustrates three reaction possibilities outlined in scheme 9.



Under similar reaction conditions the quinuclidine derivative VIII reacts to give only 20% fragmentation product IX. The chief reaction is 1,2-elimination.



The above reactions of  $\gamma$ -aminohalides do not rule out the occurrence of a concerted mechanism. It is possible that a concerted 1,4-elimination is competing with a 1,2-elimination.

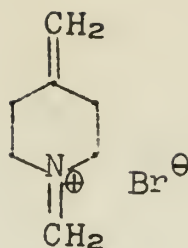
In the 4-bromoquinuclidine system X, ionization to a carbonium ion would be very difficult (28,29) and 1,2-elimination of HBr practically impossible (30). However, this compound is found to undergo solvolysis 60,000 times faster than 1-bromobicyclo[2.2.0]octane XI in 70% aqueous dioxane at 100° (31).







X



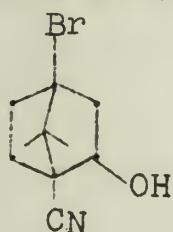
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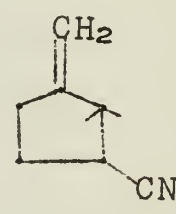
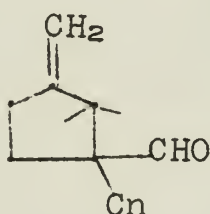
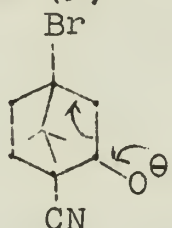
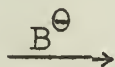
XI

The product consists entirely of the piperidine derivative XII. Thus the reaction probably proceeds through a concerted mechanism. The fragmentation is favored on stereoelectronic grounds since the lone pair on the nitrogen, the developing p-orbital at the bridgehead and the two intervening carbon atoms lie in one plane.

The solvolysis of a bridgehead halide has been observed in the case of compound XIII (32). The product is the methylenecyclopentane derivative XIV which probably arises through a fragmentation reaction similar to that of scheme (3).

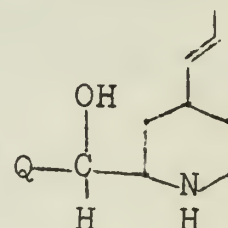
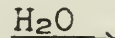
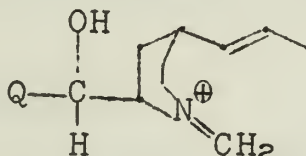
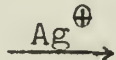
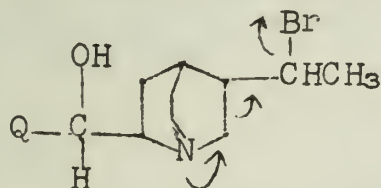


XIII



XIV

The quinine-niquine transformation (33) is an example of a quinuclidine system reacting through fragmentation.

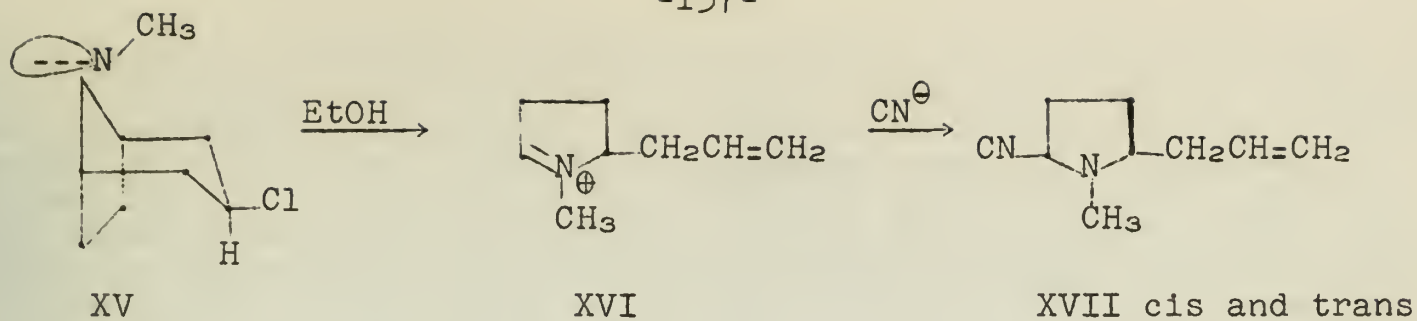


Q = 4-methoxyquinolyl

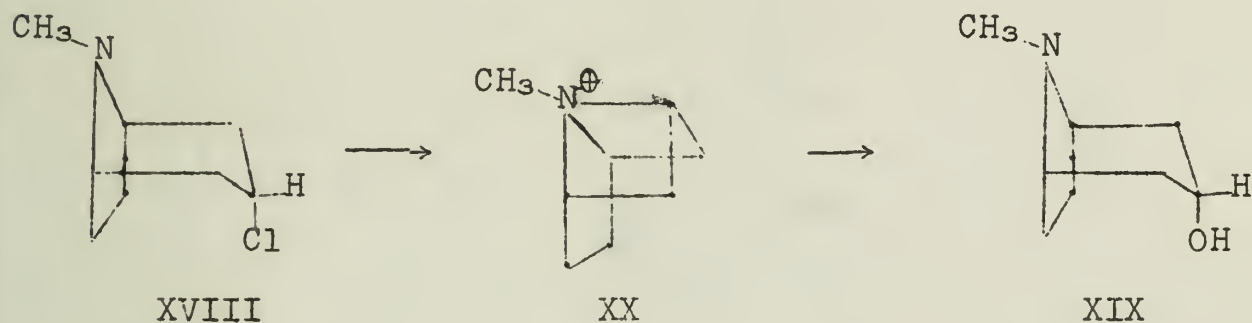
Archer (34,35,36) recently investigated the reaction of 3 $\alpha$ -chloro-tropane and its epimer with nucleophilic reagents. The  $\beta$ -epimer XV with cyanide ion in ethanol gave rise to a complex reaction, the product of which consisted entirely of the cis- and trans-isomers of 2-allyl-1-methylpyrrolidine-5-nitrile XVII. The mechanism for the reaction becomes evident if the tropane derivative is drawn in the chair form. This conformation is stereoelectronically favorable for 1,4-elimination to occur with fragmentation of the six-membered ring. Addition of cyanide ion to the resulting pyrrolinium salt XVI gives rise to the observed product XVII.







A concerted fragmentation of the 3 $\alpha$ -chlorotropene XVIII is precluded on stereoelectronic grounds when the piperidine ring is in the chair form. However, the  $\alpha$ -epimer is found to undergo solvolysis rapidly with the formation of tropine XIX showing that retention of configuration has occurred. A small amount of the olefin tropidine is also formed. Thus solvolysis is probably proceeding through two inversions at the C-3 carbon atom, the first inversion being ionization anchimerically assisted (37) by the tertiary nitrogen of the piperidine ring. This mechanism therefore suggests the ionic intermediate XX.



Grob has conducted a kinetic study of the solvolysis of the 3-tropanyl chlorides and the simpler piperidine derivative 1-methyl-4-chloropiperidine in 80% aqueous ethanol (38). His results (Table I) indicate that solvolysis of the  $\beta$ -chlorotropene involving fragmentation occurs faster than solvolysis of the  $\alpha$ -epimer which involves anchimeric assistance. Thus the driving force of fragmentation substantially succeeds that for anchimeric  $\gamma$ -nitrogen participation in this case.

Table I

Solvolysis in 80% aq. ethanol

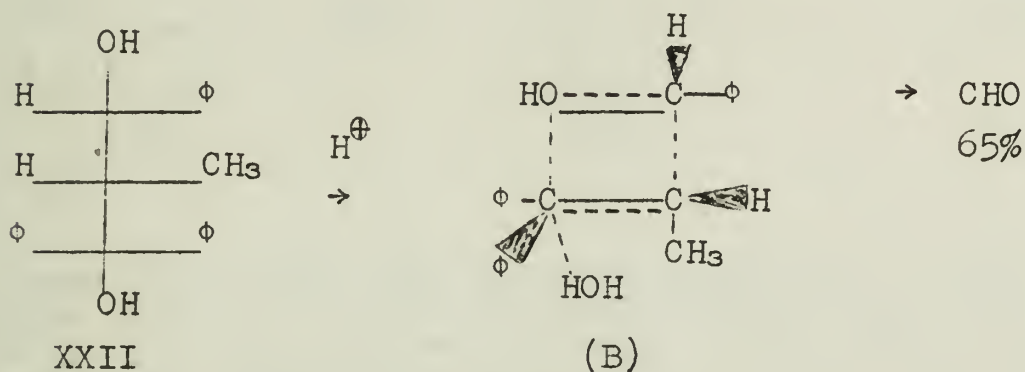
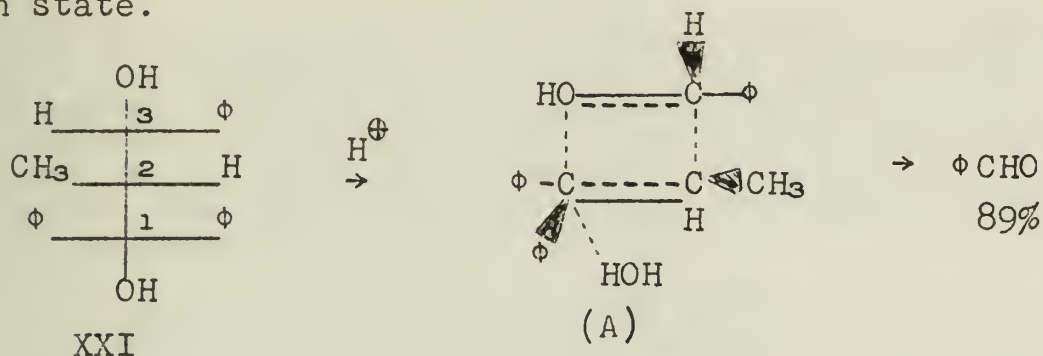
| Compound                    | $k \text{ sec}^{-1} (62^\circ)$ | $k \text{ sec}^{-1} (118^\circ, \text{Calc.})$ | $k(\text{rel.})$ |
|-----------------------------|---------------------------------|--|------------------|
| $\beta$ -epimer XV          | $3.00 \times 10^{-4}$           | $6.3 \times 10^{-2}$                           | 11,300           |
| $\alpha$ -epimer XVIII      | $7.72 \times 10^{-6}$           | $4.3 \times 10^{-3}$                           | 780              |
| 1-methyl-4-chloropiperidine | $2.06 \times 10^{-5}$           | $7.7 \times 10^{-4}$                           | 140              |
| Cyclohexyl chloride         |                                 | $5.5 \times 10^{-6} (39)$                      | 1                |

A product study of the solvolysis of 1-methyl-4-chloropiperidine has not been reported so that the mechanism is still subject to speculation.

Acid catalyzed fragmentation reactions of cyclic and acyclic 1,3-diols have been reported by Zimmerman and English (40). These authors have shown that the cleavage of the two diastereomeric



1,1,3-triphenyl-2-methyl-1,3-propanediols occurs at different rates (39). The threo isomer gave a precipitate of benzaldehyde 2,4-dinitrophenylhydrazone in 10 seconds when added to a boiling solution of the reagent in dilute acid, whereas the erythro isomer XXII required 75 seconds for the appearance of a precipitate of the hydrazone under the same conditions. The yield of benzaldehyde from the threo isomer was 89% while the erythro isomer yielded only 65% aldehyde. Both diastereoisomers yielded benzaldehyde as the only carbonyl product. These results are nicely explained by proposing a cyclic four-membered transition state.



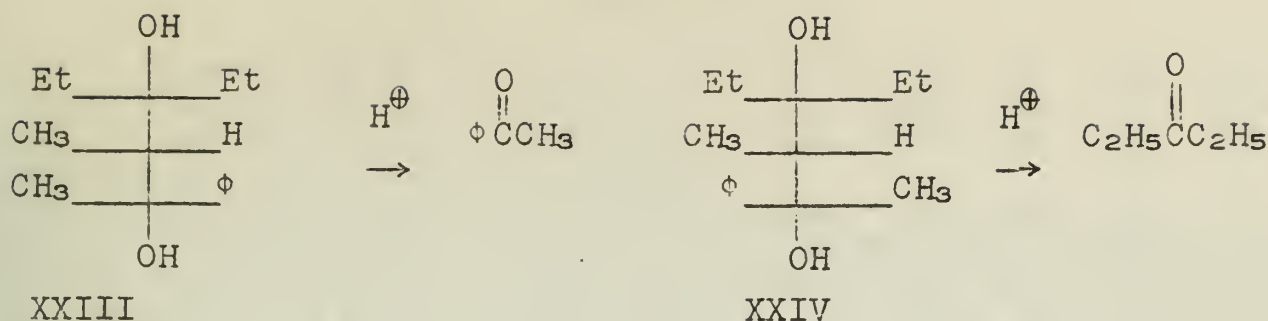
Transition state (B) is of higher free energy than (A) because of the cis orientation of the methyl and phenyl groups in (B). Thus if the difference in free energy of the transition states is greater than the difference in energy of the starting materials the threo isomer which gives rise to the less strained transition state (A) would be expected to react faster as is found in the experiment.

In the reaction of the substituted 1,3-propanediol discussed above it is seen that the cleavage proceeds exclusively in one direction, there being no benzophenone isolated. This is because the transient carbonium ion formed on protonation of the hydroxyl groups will be more stable at C-1 than at C-3 (resonance stabilization by two phenyl groups). If substitution is such that the stability of a carbonium ion at C-1 is similar to a C-3 carbonium ion then two different transition states are possible if substitution is unsymmetrical. Thus two different carbonyl compounds may be isolated. The ratio of the two carbonyl compounds will depend on the relative energies of the two transition states.

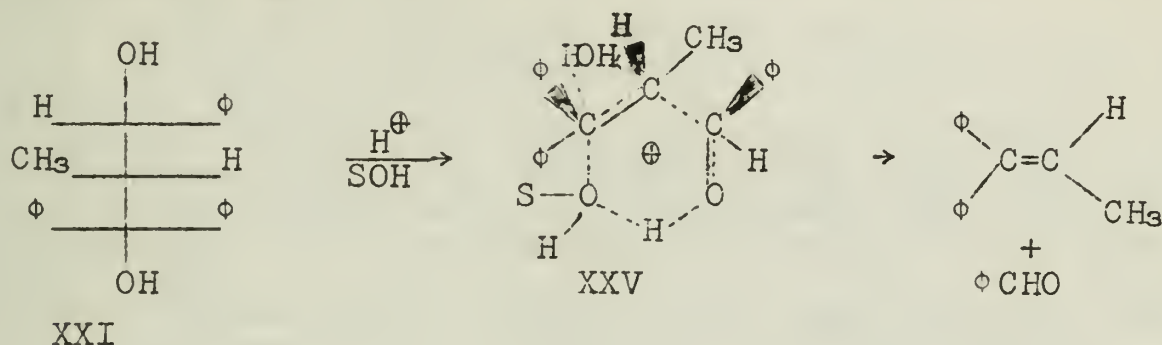
The above reasoning and the assumption of a four-membered cyclic transition state has been used to explain the fact that the diastereoisomeric 2-phenyl-3-methyl-4-ethyl-2,4-hexanediols undergo acid catalyzed cleavage to give different ketones (40). One diastereomer, presumably XXIII gives rise to acetophenone whereas the other isomer XXIV gives diethyl ketone.





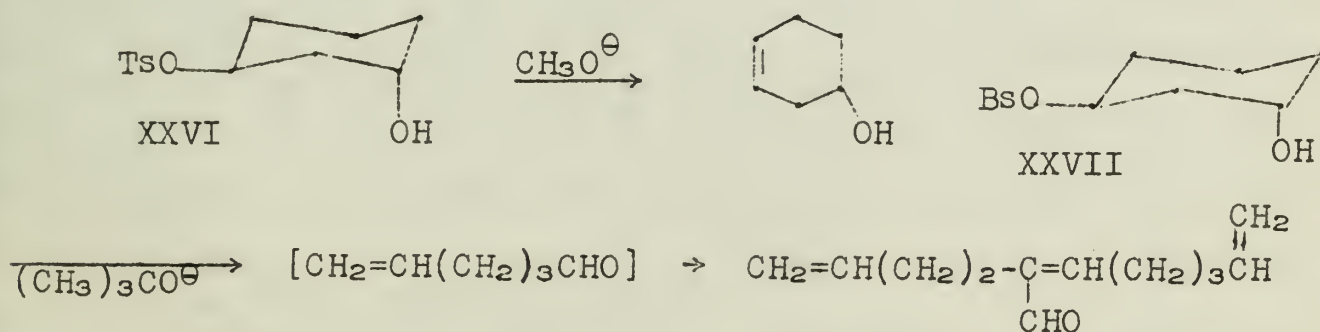


Although the cyclic transition state proposed by Zimmerman and English offers a nice explanation of the products observed in the cleavage of substituted 1,3-diols, such transition states should be considered with some reserve. A more plausible transition state would be a six-membered cyclic system involving a molecule of hydroxylic solvent. Thus a favorable transition state for isomer XXI would be XXV below in which SOH represents a molecule of solvent.



This transition state would involve less steric strain since the substituents would not be eclipsed. The unfavorable entropy factor incurred by tying up a solvent molecule in the transition state is probably more than compensated for by the favorable six-membered cyclic transition state.

Henbest (41) has reported a fragmentation to occur in the reaction of monotosylates of 1,3-diols with alkoxides. The fragmentation is assumed to depend on the formation of an intermediate anion. Thus the reaction of the monocyclic ester XXVI with methoxide ion in methanol (42) gave rise to cyclohexenol in high yield whereas the monocyclic ester XXVII when treated with *t*-butoxide in *t*-butyl alcohol yielded fragmentation products exclusively (41).



The results may be explained by assuming that in the presence of methoxide ion the concentration of secondary alkoxide ion is small whereas in the presence of *t*-butoxide the concentration is much greater. This assumption is based on the  $pK$  values of primary, secondary and tertiary alcohols (43).





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# MOLECULAR ORBITAL THEORY APPLIED TO ELECTROPHILIC SUBSTITUTION IN HETEROCYCLIC COMPOUNDS

Reported by R. G. Smith

January 5, 1959

## INTRODUCTION

This seminar is concerned with recent attempts to correlate known heterocyclic reactivity with reactivity predicted on the basis of molecular orbital (M.O.) theory. In the past few years theoretical methods have been developed which allow qualitative predictions of the structures of the main isomers formed in a given aromatic substitution reaction. These methods are not sufficiently refined to allow calculations of absolute reaction rates or to allow an accurate estimation of the relative amounts of the various isomers formed. The theoretical methods used are based on M.O. theory; accordingly a brief discussion of this theory is included below.

## Molecular Orbital Theory

Several excellent reviews on the application of M.O. theory to aromatic substitution reactions are available (1,2,3,4). The M.O. method considers the  $\pi$ -electrons of a conjugated system as occupying M.O.'s which extend completely over the conjugated system. By approximating the wave functions for the M.O.'s as linear combinations of atomic orbitals it is possible to calculate both charge distribution and  $\pi$ -electron energy for any conjugated system. In calculating these quantities it is necessary to define two integrals.

$$\begin{aligned}\alpha_i &= \text{coulomb integral} \\ \beta_{ij} &= \text{resonance integral}\end{aligned}$$

It is not possible to calculate either of these quantities and they must be evaluated by empirical means. The coulomb integral is a property of a given atom and is assumed to be the same for every atom in a conjugated hydrocarbon. The resonance integral is a property of the bond between atoms and like the coulomb integral is assumed to be the same for every bond in the conjugated system.

The coulomb and resonance integrals become of considerable importance when the M.O. method is applied to heterocycles. It becomes necessary to rely on estimated values of the coulomb integral for nitrogen while the resonance integral for the CN bond is assumed to be the same as for the CC bond. The coulomb integral can be considered as a measure of the electronegativity of an atom (1). It can be shown that the coulomb term for an atom more electronegative than carbon will be of larger negative value. Current theory indicates that  $\alpha_i$  for nitrogen can be expressed by equation I, where  $\alpha_N$  and  $\alpha_C$  are the coulomb integrals for nitrogen and carbon and  $\beta$  is the resonance integral.

$$(I) \quad \alpha_N = \alpha_C + \frac{1}{2} \beta$$

A further effect must be allowed for in treating heterocycles since the hetero atom is expected to influence the electronegativities of adjacent carbons and thus to change their coulomb integrals.

## Methods Used in Reactivity Calculations.

Two methods based on M.O. theory have been developed for comparing



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reactivities in aromatic substitution reactions. From kinetic theory rate constants may be expressed by equation II. Ideally entropies of activation should be considered in evaluating rate constants. However,

$$(II) \quad k \propto e^{-\frac{\Delta E^\ddagger}{RT}}$$

no methods are available at the present time for calculating entropies of activation and so it is assumed that the entropy term is constant for reactions involving different positions in a given molecule (1,6). Then in considering reaction at two different centers in a given molecule it is assumed that the only variable energy change will be that due to changes in  $\pi$ -electron energy. On this basis equation III can be used. In order to apply this equation to calculation of relative re-

$$(III) \quad -\log \frac{k_1}{k_2} = \frac{\Delta E_{\pi 1}^\ddagger - \Delta E_{\pi 2}^\ddagger}{RT}$$

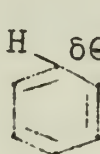
$k_1$  = rate constant for reaction at position 1

$\Delta E_{\pi 1}^\ddagger$  = change in  $\pi$ -electron energy associated with reaction at position 1.

activities a knowledge of the transition state for the reaction involved is necessary. The two methods in common use for reactivity calculations are based on idealized models of the transition state.

### Isolated Molecule Approximation

This method assumes that electrophilic substitution will occur at the position of highest electron density. The treatment is equivalent to assuming the transition state has the structure A. The attacking reagent is close to the position being attacked but not actually joined to it by a covalent bond. The charge densities necessary are readily found by M.O. theory. A theoretical justification of the relationship between reactivity and charge distribution has been given by Coulson and Longuet-Higgins (8,9).



A

### Localization Energy Method

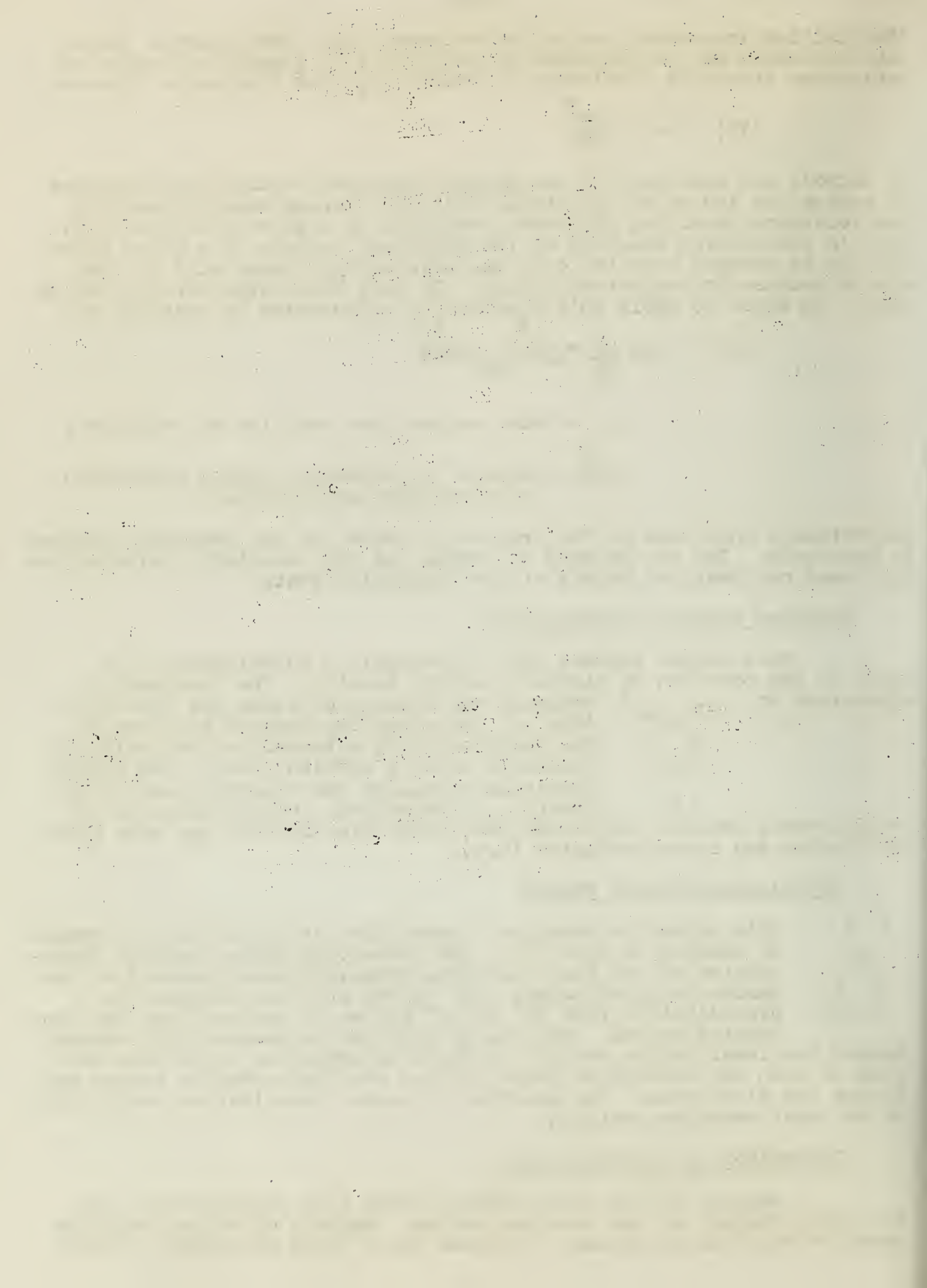


B

This method is based on a transition state (B) first proposed by Wheland in 1942 (7). The transition state involves localization of two electrons (electrophilic substitution) on the carbon being attacked. The carbon attacked changes its hybridization from  $sp^2$  to  $sp^3$  and so is removed from the conjugated system. The energy required to produce this charge, termed the localization energy, is found by computing  $\pi$ -electron energies of both the transition state and the starting aromatic system and taking the difference. The position of lowest localization energy will be the most reactive position.

### Comparison of Approximations

Neither of the above methods takes into consideration the attacking reagent or the reaction medium. Neglect of reagent effects seems to be a fairly serious criticism since cases are known in which





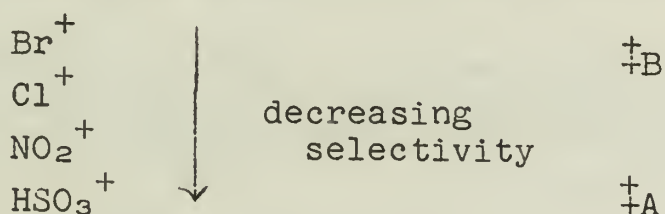
different electrophilic reagents attack different positions. Thus dibenzofuran (12) is nitrated in the 3-position while some other electrophilic reagents attack the 2-position. The effect appears to be due to reagent and can be explained by use of the Hammond postulate. The reagent is regarded as controlling the actual form of the transition state which with some reagents will be approximated by model A while with other reagents will be approximated by model B (3,20). It follows that in cases where the two approximations disagree it is possible that different electrophilic reagents may substitute in different positions.

Experimental justification has been provided for the above picture of reagent effects by H. C. Brown (10,11). Brown ran electrophilic substitution reactions with a variety of reagents on mixtures of benzene and toluene. Certain reagents, classified as reagents of low reactivity, were found to be highly selective in attacking toluene in preference to benzene and these reagents were also found to give relatively small amounts of meta isomer in their reaction with toluene. By contrast, other reagents, classified as reagents of high reactivity, were found to be of low selectivity and to give relatively large amounts of meta isomer with toluene. The fact that reagents of low reactivity are highly selective was taken as evidence that the transition state for toluene receives aid from hyperconjugation and hence that it resembles a tetrahedral configuration at the atom attacked.



Conversely, a low selectivity indicates that the transition state is reached before the tetrahedral configuration is attained. Therefore highly selective reagents

should have a transition state closely approximated by structure B, while reagents of low selectivity should have one closely approximated by structure A. The common electrophilic reagents arranged in order of decreasing selectivity are presented below.



A method of predicting reactivities, which takes reagent into account, has recently been developed by Dewar (13).

### Influence of Reaction Medium

In considering reactivity of heterocycles attention must be paid to reaction conditions. In nitrogen heterocycles, for example, electrophilic substitution in acid media will be occurring on the cation, while in base the substitution may occur on the anion. These changes on the nitrogen atom result in a corresponding change in electronegativity of the nitrogen and hence a change in the coulomb integral for nitrogen. Thus an allowance must be made for this factor when doing M.O. calculations on heterocycles.

A comprehensive survey of the effects of medium has been reported by R. D. Brown (1,12,14,15,16), who allows for variations

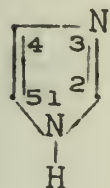




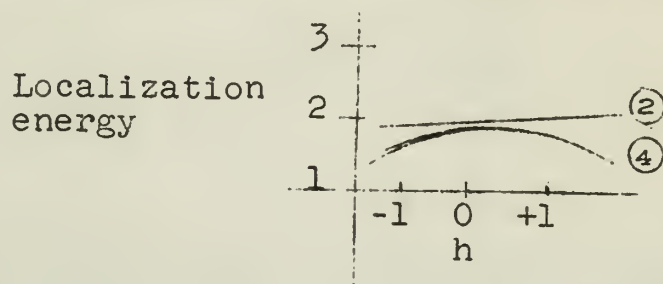
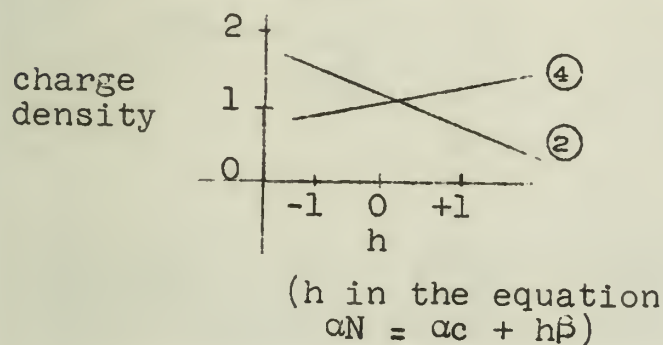
in the nitrogen coulomb term by use of the equation below, wherein  $h$

$$\alpha_N = \alpha_C + h\beta$$

is a numerical coefficient whose value can be varied to take account of all possible values of  $\alpha_N$ . The treatment used assumes that effects of nitrogen on the coulomb integrals of adjacent carbons can be neglected and that resonance integrals for CC and CN bonds are the same. Glyoxaline presents a particularly interesting example.



Experimentally it is known that nitration, bromination and sulfonation, which are done in acid media, occur at the 4-position, while diazonium coupling and iodination, which are done in basic media, occur at the 2-position. Charge densities and localization energies are shown in the two diagrams below.



For positive values of  $h$  both charge densities and localization energies predict substitution in the 4-position which is in agreement with the nitration, bromination and sulfonation results. The observed diazonium coupling and iodination in the 2-position can be explained as due to reaction medium effects. If it is assumed that in basic solution the reaction occurs on the glyoxaline anion and further that negatively charged nitrogen is less electronegative than carbon the observed orientation can be explained by the fact that for negative  $h$  charge densities predict substitution in the 2-position.

The assumption that diazonium coupling occurs by attack on the glyoxaline anion has been confirmed by kinetic studies (17). The kinetics of the reaction were found to be pseudo second order leaving as possible mechanism

- a)  $\text{ArN}_2^+ + \text{glyoxaline}$
- b)  $\text{ArN}_2^+ + \text{glyoxaline anion}$ .

These two mechanisms were differentiated by comparing the experimental pH-vs.-rate curve with the theoretical curves calculated for the two possible mechanisms. The result of this comparison showed mechanism b to be the correct one.

### Dewar's Theory

A method of predicting reactivities has been developed by Dewar (4,13,18) which takes account of reagent influences. Dewar starts by assuming Wheland's model as correct for aromatic substitution reactions. Perturbation theory is used to develop an equation which can be used to calculate activation energies for aromatic substitution reactions. The theory applies only to a class of hydrocarbons known as alternant hydrocarbons. An alternant



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hydrocarbon (21) is one in which the atoms making up the conjugated system can be divided into two sets, starred and unstarred, such that no two atoms of like type are directly linked. Naphthalene is an example of this type of aromatic hydrocarbon. Alternant hydrocarbon (A.H.) can be further classified into even A.H.'s (containing an even number of conjugated atoms) and odd A.H.'s. If Wheland's model is assumed for the transition state then the starting aromatic is an even A.H. while the transition state is an odd A.H. An even A.H. has an even number of M.O.'s and so all are paired (Fig. I). The number of electrons is just sufficient to fill, in pairs, half the available M.O.'s. On the other hand, an odd A.H. (Fig. II) has an

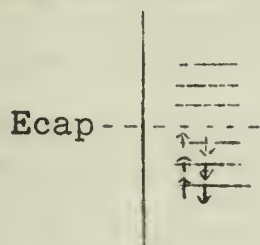
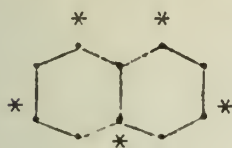


Fig. I

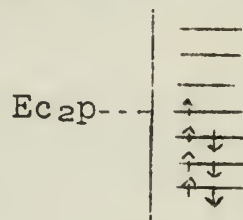


Fig. II

odd number of M.O.'s and so one M.O. is unpaired and has the same energy as a carbon 2p A.O. This unpaired M.O. is referred to as the non-bonding molecular orbital (NBMO).

When perturbation theory is applied to alternant hydrocarbons, the  $\pi$ -electron energy required to attain Wheland's transition state is expressed by equation 1. The mathematics involved are quite complex and will not be considered in this seminar.

$$(1) \Delta E_{\pi} = Cx - 2\beta(A_{or} + A_{os}) = Cx - \beta N_t$$

$A_{or}$  and  $A_{os}$  - coefficients of the NBMO on the atoms adjacent to the position attacked

$Cx$  - constant

$N_t = 2(A_{or} + A_{os})$

Then the reactivities of the various positions in a given molecule can be compared by calculating values of  $2\beta(A_{or} + A_{os})$ . In order to apply this equation a method is necessary to determine the values of  $A_{or}$  and  $A_{os}$ . A simple method is available based on rules developed by Lönquett-Higgins (19).

$$1) A_{oi} = 0 \text{ if } i \text{ is unstarred}$$

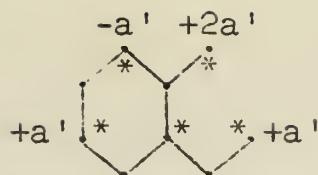
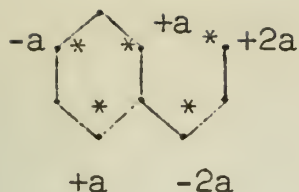
$$2) \sum_k A_{ok} = 0 \text{ the sum being over atoms } k \text{ attached to a given unstarred atom } i.$$

$$3) \sum_j A_{oj}^2 = 1 \text{ summed over all atoms.}$$

We are now in a position to calculate relative reactivities in any polycyclic system and naphthalene is given below as a typical example.







$\alpha$  - substitution  
From rule 3  $a = 1/\sqrt{11}$   
 $\Delta E\pi = 2\beta(3a) = 1.81\beta$

$\beta$  - substitution  
From rule 3  $a' = 1/\sqrt{8}$   
 $\Delta E\pi = 2.12\beta$

The calculations indicate that the  $\alpha$ -position is preferred, which is known to be the actual case. The calculations apply only in cases where the product is kinetically controlled.

Dewar's equation can be justified by plotting activation energies obtained from it against those obtained by the molecular orbital method (13). A straight line plot is obtained indicating that the method is at least as good as the M.O. method.

The fact that the method allows for reagent influences is not immediately apparent and was not introduced until some years after the original theory had been postulated (20). Neglecting entropy effects the following equations can be written.

$$\log k_i = Cx - \frac{(\Delta E\pi)_i}{RT} = Cx + \frac{2\beta(A_{or} + A_{os})}{RT}$$

$$\log \frac{k_i}{k_o} = \frac{\beta(N_i - N_o)}{RT}$$

$k_o$  = rate constant for substitution in benzene  
 $N_o$  = reactivity number for a benzene position.

On this basis a plot of log relative reactivities against  $2(A_{or} + A_{os})$  should give a straight line of slope  $\beta/RT$ . Such a plot was constructed (24) from nitration data on various polycyclic compounds and a straight line was obtained. However,  $\beta$  (resonance integral) was found to have a value of -6 kcal. which is considerably smaller in absolute magnitude than the commonly accepted value of -20 kcal. Plots for other reagents were found to give different values of  $\beta$ .

Dewar explains the above observations on the assumption that Wheland's transition state is actually an intermediate. Then the success of the method must depend on a linear correlation between activation energy and heat of reaction. The  $\beta$  term in the above equations becomes an empirical parameter and can be correlated with reactivity of the reagent. It is readily seen that the smaller  $\beta$ , the smaller the differences in reactivities of the positions. Therefore reagents of low selectivity have low  $\beta$  values.

The theory can easily be extended to heterocycles by making use of some work due to Lonquet-Higgins (19). Lonquet-Higgins has shown that the equation below can be applied to alternant heterocycles to determine their energy from the corresponding energy of the analogous carbocycle. The form shown applies only to electrophilic substitution reactions.



$$\Delta E = \Delta E_0 + \sum_r \alpha r a_{or}^2$$

$\Delta E$  = activation energy for heterocycle

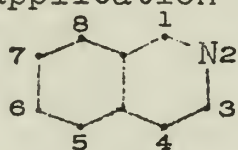
$\Delta E_0$  = corresponding activation energy of the carbocycle

$\alpha r$  = coulomb integral for atom  $r$

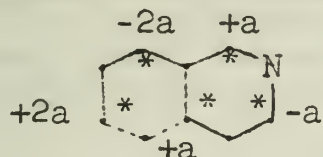
$a_{or}$  = NBMO coefficient for atom  $r$  in the transition state

A knowledge of the relationship between the various coulomb terms is necessary and Dewar uses the approximation that if  $\alpha$  is the coulomb term for nitrogen, then  $1/3\alpha$  is the value for carbons adjacent to nitrogen and 0 is the value for all other carbons (5).

As an example of the application of the method isoquinoline is considered (21). Consider substitution at the 5-position. Our previous calculations on naphthalene have shown that  $\Delta E_0 = 1.81 \beta$  for this position. The transition state with



appropriate coefficients is represented below.



$$a = \frac{1}{\sqrt{11}}$$

$$\Delta E_{\pi} = 1.81 \beta + a^2 \frac{\alpha}{3} + a^2 \frac{\alpha}{3}$$

$$= 1.81 \beta + .059\alpha$$

In a similar manner the value for substitution in the 8-position is found to be  $1.81 \beta + .091 \alpha$ .

Before proceeding further it is necessary to obtain experimental values for  $\alpha$  and  $\beta$ . The value for  $\beta$  has been determined previously (24) from nitration work on hydrocarbon systems and for nitration in acetic anhydride has the value -6 kcal. Dewar (21) estimates a value of -4 kcal. for nitration in sulfuric acid. The value for  $\alpha$  was determined from the relative amounts of nitration products formed on nitrating isoquinoline (21). At 100° C. isoquinoline was found to yield 84.8% 5-nitro derivative and 15.2% 8-nitro derivative. Then the difference in activation energy  $\Delta E_8 - \Delta E_5$  can be found by using

$$\log \frac{k_5}{k_8} = \frac{\delta \Delta E_{\pi}}{RT}$$

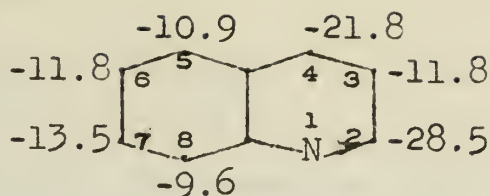
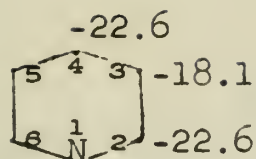
$$\delta \Delta E_{\pi} = \Delta E_8 - \Delta E_5$$

The activation energy calculated on this basis is -1.27 kcal. Our calculations show that  $\delta \Delta E_{\pi}$  can also be expressed as  $.032\alpha$ . Then  $\alpha$  must have the value -40 kcal. These values for  $\alpha$  and  $\beta$  apply only to nitration in sulfuric acid where the nitrogen can be considered as protonated. Different values would be necessary when considering electrophilic substitutions, other than nitration.

The relative activation energies calculated for pyridine and quinoline, using the above values for  $\alpha$  and  $\beta$ , are shown in the diagrams below.

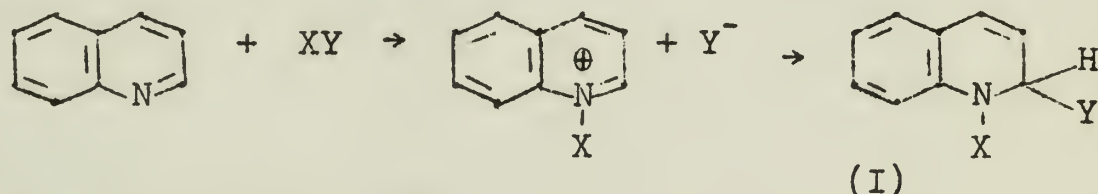






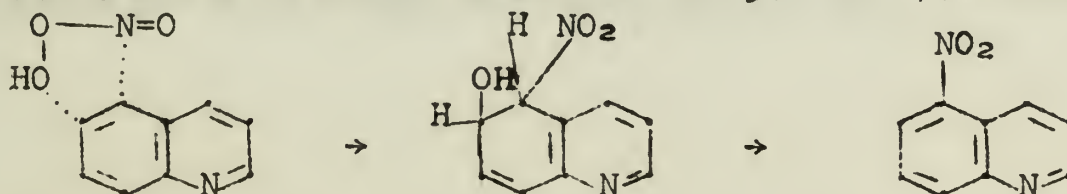
Nitration data has been reported for both these compounds (21,25). Quinoline at 0°C. is found to yield approximately equal amounts of 5 and 8 isomers, while pyridine although considerably more difficult to nitrate yields the 3-nitro derivative. The results are in good agreement with theory and the relatively difficult pyridine nitration can be explained on the basis of its high energies of activation.

There are several instances in the literature reporting formation of the 7-nitro derivative of quinoline. A reinvestigation of these reactions was reported by Dewar (22) since this derivative is unexpected on the basis of Dewar's theory. Dewar found that the use of lithium nitrate in acetic anhydride gave, not the 7-derivative as previously reported but a mixture of the 3,6 and 8 derivatives. Nitric acid in acetic anhydride at 20°C. was found to give only the 3-derivative while nitric acid in trifluoroacetic acid gave only the 6 and 8 derivatives. However, these results appear to be just as difficult to understand as 7-substitution since there is no reason to expect 3-substitution in preference to 5-substitution. Dewar (22) suggests that in these cases the entity being nitrated is not quinoline itself but a 1,2-dihydroquinoline derivative.



The nature of XY is not known but may be an acyl nitrate. The adduct I is an aniline derivative and so should nitrate in positions ortho and para to nitrogen (6<sup>and</sup> 8 positions). The 3-derivative would result from addition of oxides of nitrogen to the styrene like double bond followed by elimination. This is in line with the fact that nitration in trifluoroacetic acid gave no 3-derivative since oxides of nitrogen should not be present in trifluoroacetic acid which is a non-reducing solvent.

However, some of the cases reporting 7-nitro derivatives were verified. The use of pernitrous acid at 0°C. produced the 5, 6, 7 and 8 isomers in roughly equal amounts. This result is also in disagreement with theory and a second mechanism was proposed for nitrations involving pernitrous acid. It is proposed that pernitrous acid behaves like ozone which is known to add to the 5:6 and 7:8 bonds of quinoline.



The accuracy of the theory in predicting partial rate factors was also tested in the case of quinoline. From the experimental isomer ratio it is found that

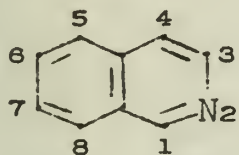




$$\frac{k_5 \text{ nitroisoquinoline}}{k_5 \text{ nitroquinoline}} = \frac{46.4}{1}$$

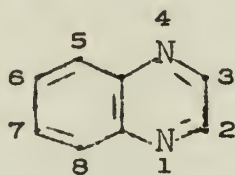
The value calculate from energy difference between the two positions is 10.5:1.

Calculations were performed on a variety of heterocycles (21). The order of reactivity, predicted from these calculations is listed below each diagram.



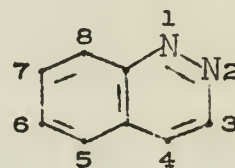
Isoquinoline

5 > 8 > 7



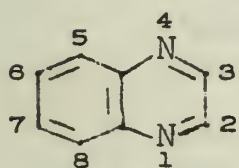
Quinoxaline

5 = 8 >> 6 = 7



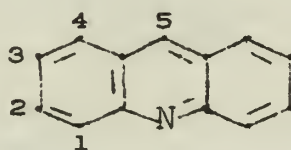
Quinazoline

8 >> 6 > 5



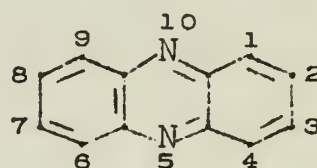
Cinnoline

5 = 8 >> 6 = 7



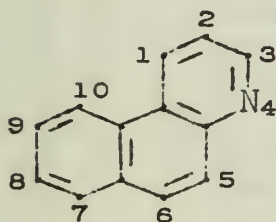
Acridine

1 > 3 >> 4



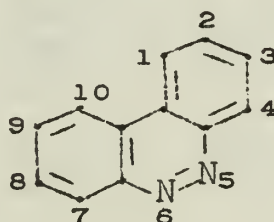
Phenazine

1 > 2



Benzoquinoline

5 > 7 > 9 = 10



Benzocinnoline

1 > 3 >> 4

Isoquinoline was found (21) to nitrate mainly in the 5-position with a small amount of 8-nitration. Quinoxaline (26) yields the 5-nitro derivative as the only mononitration product.

The most recent paper by Dewar (23) contains work on nonalternant hydrocarbons and heterocycles. An extension of the theory to non-alternant hydrocarbons has not yet been published but Dewar (23) indicates that such a study has been undertaken.

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# SOLVENT EFFECTS IN FREE RADICAL REACTIONS

Reported by J. A. Kampmeier

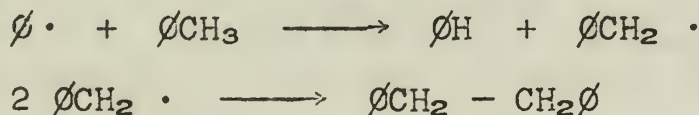
January 8, 1959

## INTRODUCTION

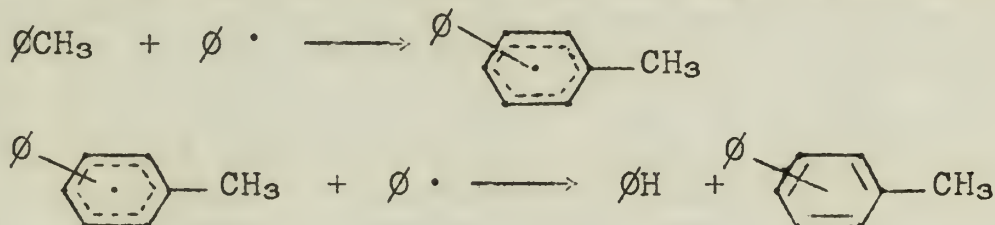
Positive identification and evaluation of the role of solvents in reactions involving free radical intermediates has long been delayed. Although intermolecular forces are not limited to those of an electrostatic nature (1), correlations between solvent polarity, dielectric constant and radical behavior have frequently been sought (2,3,4,5,6). Such relationships have been observed, but the effects are small and apparently not of major importance (7,8,9). In some cases the data were not sufficiently resolved to permit a cogent interpretation (compare 10,11,12).

More recently, however, complexes of highly electrophilic radicals with electron rich substrates have been postulated (13,14, 15,16,17). The expressed aim of this seminar is a discussion of these complexes and their effect on the course of radical reactions.

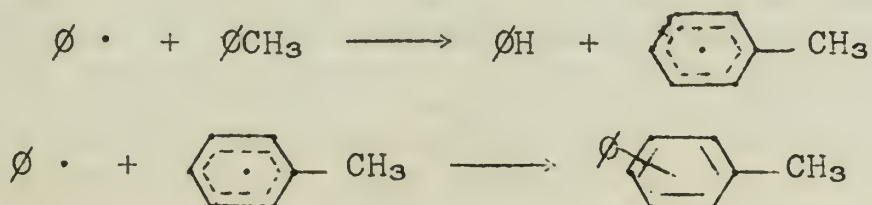
Studies by Szwarc of the reaction of phenyl radical with toluene in solution and in the vapor phase have led to the conclusion that these two systems are basically different (13). In the vapor phase a benzylic hydrogen atom is abstracted from toluene and the theoretical quantities of dibenzyl and benzene are obtained. In



toluene solution no dibenzyl is formed; only the isomeric methyl-biphenyls are obtained. Two reaction schemes may be written. In the first, toluene may undergo radical substitution followed by hydrogen atom loss. Alternatively, phenyl radical might abstract an aromatic



hydrogen atom from toluene. The radical formed in this fashion could then combine with another phenyl radical to form the requisite methyl-



biphenyl. However, the greater bond dissociation energy of an aromatic hydrogen atom compared with a benzylic hydrogen atom (18)

The following report describes the results of the research carried out during the year 1950-1951. The work was done in the Department of Chemistry, University of Chicago, under the supervision of Professor [Name]. The research was supported by the National Science Foundation, Grant No. [Number].

The work was carried out in the laboratory of Professor [Name], who is grateful to the National Science Foundation for the grant which made this work possible. The author wishes to express his appreciation to Professor [Name] for his helpful suggestions and criticisms. The author also wishes to thank the following persons for their assistance during the course of the work: [Names].

CHICAGO, ILLINOIS

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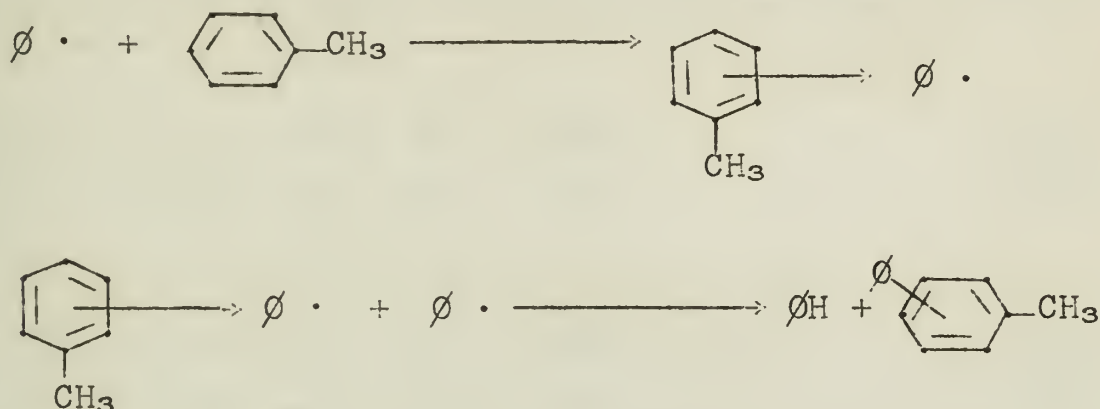
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renders this latter mechanism improbable.

In order to rationalize the different reaction pathways observed in the liquid and vapor phases, a  $\pi$ -complex involving toluene and the phenyl radical was suggested. It now remains only to assign to this complex a lifetime sufficiently great to permit hydrogen abstraction. A less stable complex might simply act as a source of phenyl radicals of somewhat reduced reactivity. The reaction may be expressed as follows:



In the vapor phase complete dissociation of the complex would be anticipated. It seems not unlikely, therefore, that attack of a free phenyl radical on the benzylic hydrogens of toluene would be obtained. Similar complexes have been postulated as explanation for phenomena observed in the polymerization of styrene in the presence of bromobenzene (16), in the inhibition of autoxidation processes by aromatic compounds (14,15) and in the radical chlorination of cumene (17).

#### PHOTOCHLORINATION OF 2,3-DIMETHYL BUTANE

G. A. Russell has performed a thorough dissection of the photochlorination of 2,3-dimethylbutane in various solvents (12,19). All chlorinations were performed in the presence of a large excess of hydrocarbon for approximately 50 minutes. The minimum ratio of chlorine to 2,3-dimethylbutane employed was 1 to 20. Reactions were carried out in the presence of light. The temperature of the reaction was varied from 25° to 55°. Product compositions, determined by means of vapor phase chromatography, showed only two compounds to be present: 1-chloro-2,3-dimethylbutane and 2-chloro-2,3-dimethylbutane. These products correspond to an apparent substitution of a chlorine atom for a primary and a tertiary hydrogen atom.

The most significant result of these experiments is that the ratios of alkyl chlorides formed are influenced dramatically by the presence of certain solvents. In the photochlorination of neat 2,3-dimethylbutane, 60% of 1-chloro-2,3-dimethylbutane and 40% of 2-chloro-2,3-dimethylbutane are obtained. In 12 M carbon disulfide or 8 M benzene solution, more than 90% of the 2-isomer is formed. The synthetic applications of this discovery require little elucidation.

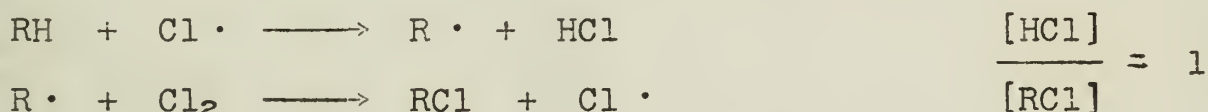
At first glance, these data would seem to indicate that the product formed by attack at a tertiary hydrogen is favored by the presence of certain solvents. However, certain alternative possibilities must be eliminated before this conclusion becomes

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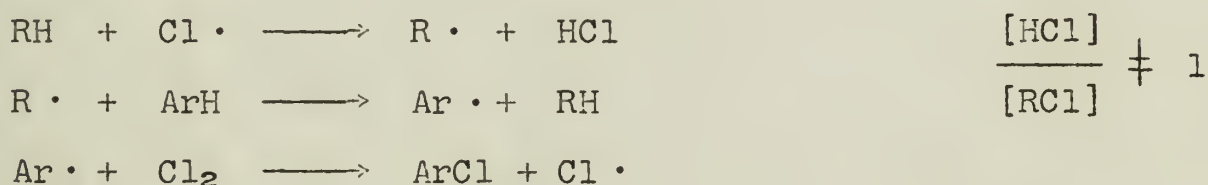
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justifiable. A process in which a solvent molecule reacts preferentially with one of the alkyl radicals (e.g. the primary radical) would lead to the formation of a chlorinated solvent molecule. In the photochlorination reaction in benzene solution, no chlorobenzene could be detected in the product mixture. Further substantiation of the absence of this reaction was found in the quantities of alkyl chloride and hydrogen chloride formed. They were obtained in a 1:1 mole ratio. This ratio can be obtained only if each alkyl radical reacts to form alkyl chloride. Any diversion of alkyl radicals by reaction with solvent should produce a significant deviation from this ratio. The propagation steps in each case are as follows.



But,



The probability of a hydrogen migration is small (20). Nevertheless, this alternative was readily dispatched by an examination of the product ratios in the photochlorination of 2-deuterio-2-methylpropane (12). In the absence of added solvent the deuterium chloride, hydrogen chloride ratio was found to be 2.9:9, while the *t*-butyl and isobutyl chloride ratio was 3.5:9. In 5.9 M chlorobenzene solution, the ratios found were 14:9 and 18:9 respectively. The constancy of these ratios indicates that relatively little, if any, hydrogen rearrangement has occurred.

The preceding discussion leads to the conclusion that the products formed in the photochlorination of 2,3-dimethylbutane are indeed a true measure of the point of attack of the chlorine atom on the hydrocarbon. A comparison of the relative reactivities of the tertiary and primary hydrogen atoms of 2,3-dimethylbutane is now justifiable. These reactivity ratios (statistically corrected) are tabulated below.

TABLE I

| Solvent                 | Solvent Concentration<br>(moles/liter at 25°) | Relative Reactivity (tert./prim.) |     |     |
|-------------------------|---|-----------------------------------|-----|-----|
|                         |   | 25°                               | 40° | 55° |
| 2,3-dimethylbutane      | 7.6   | 4.2                               | 3.9 | 3.7 |
| carbon tetrachloride    | 4.0   |                                   |     | 3.5 |
| cyclohexane             | 4.0   |                                   |     | 3.6 |
| propionitrile           | 4.0   |                                   |     | 4.0 |
| <i>t</i> -butyl alcohol | 4.0   |                                   |     | 4.8 |
| dioxane                 | 4.0   |                                   |     | 5.6 |
| <i>n</i> -butyl ether   | 4.0   |                                   |     | 7.2 |
| dimethylformamide       | 4.0   |                                   |     | 9.1 |
| carbon disulfide        | 4.0   |                                   |     |     |



1. The first group of people who are interested in the study of the history of the world are the historians. They are people who study the past and try to understand what happened and why it happened. They use a variety of sources, including books, documents, and artifacts, to reconstruct the past. They also try to understand the people who lived in the past and how they thought and felt. Historians are interested in the past for a variety of reasons. Some are interested in the past because they want to know what happened and why it happened. Others are interested in the past because they want to understand the people who lived in the past and how they thought and felt. Still others are interested in the past because they want to learn from the mistakes of the past and avoid them in the future.

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*Journal of Management Studies*, 19(1), 67-80.

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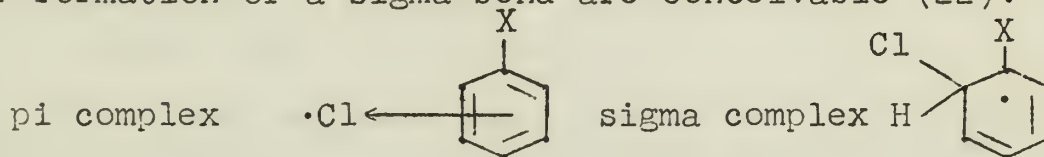
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|                          |      |      |      |      |
|--------------------------|------|------|------|------|
| carbon disulfide (cont.) | 8.0  | 106  |      |      |
|                          | 12.0 | 225  |      |      |
| nitrobenzene             | 4.0  |      |      | 4.9  |
| benzotrifluoride         | 4.0  |      |      | 6.9  |
| methyl benzoate          | 4.0  |      |      | 10.2 |
| chlorobenzene            | 4.0  | 17.1 | 13.5 | 10.2 |
|                          | 6.0  | 27.5 |      |      |
| benzene                  | 4.0  | 20   | 17.0 | 14.6 |
|                          | 8.0  | 49   | 40   | 32   |
| toluene                  | 4.0  |      |      | 15.4 |
| anisole                  | 4.0  |      |      | 18.4 |
| cumene                   | 4.0  |      |      | 20.3 |
| <u>t</u> -butylbenzene   | 4.0  | 35   |      | 24   |
| mesitylene               | 4.0  |      |      | 25   |
| iodobenzene              | 4.0  |      |      | 31   |
| diphenyl sulfide         | 2.0  |      |      | 24   |
| diphenyl ether           | 2.0  |      |      | 10.3 |

An examination of these data reveals the following relevancies. Most outstanding, as noted before, is the dramatic effect of the solvent on the relative reactivities of the tertiary and primary hydrogen atoms of 2,3-dimethylbutane. Aromatic solvents, in general, seem most consistent in their ability to alter relative reactivities. The magnitude of the effect is a function of the solvent concentration and seems to be inversely related to the reaction temperature. Finally, a lack of correlation between solvent polarities and relative reactivities is evident.

Rates of hydrogen abstraction by chlorine atoms have long been known to vary primary < secondary < tertiary (21). It is seen that the preference of a chlorine atom for a tertiary hydrogen is greatly enhanced in aromatic solvents. This enhanced selectivity suggests a reagent less reactive than the free chlorine atom. Furthermore, an examination of Table I reveals an apparent correlation between the selectivity of the reagent and the electron density of the aromatic ring. Such observations are suggestive of a complexing type interaction between the aromatic ring and the electrophilic chlorine atom. Complexes involving either the pi-cloud of the aromatic nucleus or formation of a sigma bond are conceivable (22).



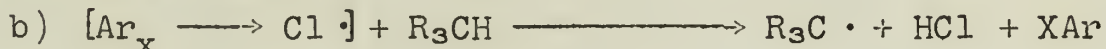
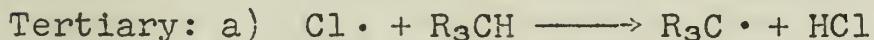
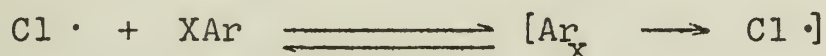
Several strong arguments mitigate the probability of a sigma complex. The stability of such a complex should be determined by resonance interactions with substituent groups. Such being the case, a correlation between relative reactivities in photochlorination and rates of radical aromatic substitution should be apparent. In fact, any such correlation is lacking. Relative rates of aromatic phenylation decrease as follows: nitrobenzene > anisole > toluene > chlorobenzene > benzene > t-butylbenzene (23). Relative reactivities in photochlorination decrease t-butylbenzene > anisole > toluene > benzene > chlorobenzene. A similar lack of correlation with methyl affinities is observed (24). One would also expect sigma complex formation to lead to chlorinated aromatic products. It has been previously noted that this does not occur.





The abilities of aromatic rings to act as electron donors in  $\pi$ -complex formation with electrophilic species are well documented (25). Silver ion is known to complex with aromatic rings in aqueous solution to give complexes whose stabilities are correlated (26) by Hammett's  $\sigma_m$  function (27). The relative basicities of aromatic rings have been determined by an examination of the equilibrium constants involved in  $\pi$ -complex formation at low temperature between an aromatic ring and hydrochloric acid (22). Again, the stabilities are determined by the electron densities of the rings involved as are the stabilities of complexes of molecular iodine with aromatic rings (28).

The formation of  $\pi$ -complexes between aromatic rings and a variety of acceptors has been found to be exothermic by a factor of 1-4 kcal/mole (25). Russell has estimated a minimum heat of formation of -1.2 kcal./mole for a 1:1 benzene to chlorine atom complex. These data lead to the reasonable proposition that the reactivity of a  $\pi$ -complex should be less (and the selectivity greater) than that of a free chlorine atom. This conclusion also follows readily from a consideration of the relative degrees of resonance stabilization of a free and complexed chlorine atom. It is also reasonable to expect the reactivity of the complexed chlorine atom to be inversely related to the stability of the complex. When relative reactivities are plotted against relative basicities of aromatic nuclei as determined above, or Hammett's  $\sigma_m$  function, a linear relationship is observed. These correlations form strong arguments in support of complexing of a  $\pi$ -type between aromatic nuclei and free radicals. The mechanism of chain propagation may now be written.



The effect of certain non-aromatic solvents may be incorporated into the foregoing argument (12). Alternatively, in some cases, radical addition may occur to produce a new, less reactive radical (12). Chlorination with sulfonyl chloride is an excellent example of this latter phenomenon.

Of the relevancies gleaned from Table I, those related to reaction temperature and solvent concentration remain unconsidered. Comparison of relative reactivity ratios of a free chlorine atom at 25°, 40° and 55° gives a value for the difference in activation energies for primary and tertiary hydrogen abstraction of 0.7 kcal./mole. A similar treatment when 4 M benzene is present gives a difference,  $E_p - E_t$ , of 2.7 kcal./mole. These data offer further

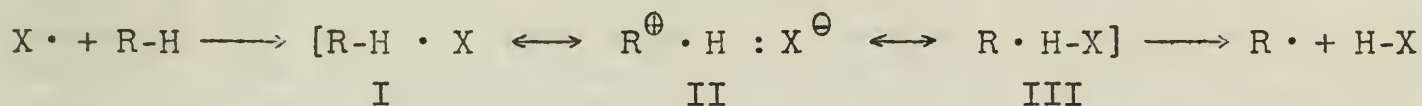




corroboration of the statement that a complexed chlorine atom is more selective than a free chlorine atom. It is not surprising that the selectivity of a complexed chlorine atom decreases as the reaction temperature increases. This observation is in accord with the general Boltzmann phenomenon; i.e., an increase in temperature results in an increase in the number of chlorine atoms having sufficient energy to attack a primary hydrogen atom.

The effect of solvent concentration on the magnitude of the solvent effect is by no means clear. It is apparent that solvent effects increase in a non-linear fashion with concentration increases. Complexes of the  $\pi$ -type are known involving more than one aryl ring. Silver ion, for example, is found to form both 1:1 and 1:2 complexes with toluene and a variety of other aromatic hydrocarbons (25). The reactivity of the complex should decrease as the number of aryl groups increases. Such phenomena probably account for the increased selectivity observed at high solvent concentrations.

The preference of a chlorine atom for a tertiary hydrogen atom has been previously mentioned. This observation may be rationalized by a consideration of both a polar and a resonance effect. The polar effect, in essence, predicts that the chlorine atom will attack at the site which will yield the most stable carbonium ion. The resonance effect implies that the radical with the greatest amount of resonance energy will be favored. The transition state for the reaction may be considered as a resonance hybrid.



If the contribution of III to the hybrid is great, it is expected that the resonance energy of the resultant radical will be important in product determination. On the other hand, if I and II are the major contributors, then the availability of electrons in any particular bond will be determinant. The Hammond principle (29) predicts that structure I will be the major contributor when the radical is highly reactive (i.e. free chlorine atoms). A correspondingly greater contribution from II and III will be expected with radicals of lesser reactivity (i.e. complexed chlorine atoms). The problem to be considered may be stated thus. Does the complexing of a chlorine atom increase the importance of structure II or III in the hybrid transition state? An increase in the contribution of either II or III will result in the observed enhanced selectivity of the complexed chlorine atom. Russell has directed his attentions to this problem (30). Competitive chlorinations in a variety of solvents were performed in a manner similar to that already described. The data from these experiments permitted a comparison of the relative reactivities of a series of carbon-hydrogen bonds. A reactivity of 1.0 was assigned to the primary hydrogen atom of 2,3-dimethylbutane.

In order to determine the magnitude of the polar effect, compounds were compared whose radicals possessed approximately equivalent amounts of resonance stabilization, but whose reactivities varied significantly because of differences in the availability of electrons. The following data are instructive.



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## Relative Reactivity

| <u>Substrate</u>           | <u>No solvent</u> | <u>4 M Benzene</u> | <u>4 M <i>t</i>-butyl-<br/>benzene</u> | <u>12 M CS<sub>2</sub></u> |
|----------------------------|-------------------|--------------------|--|----------------------------|
| tetramethylsilane          | 1.1               | --                 | 1.1                                    | 0.96                       |
| trimethylchloro-<br>silane | 0.17              | 0.16               | 0.16                                   | 0.20                       |
| 2,3-dimethyl-<br>butane    | 1.0               | 1.0                | 1.0                                    | 1.0                        |
| acetonitrile               | 0.004             | 0.003              | --                                     | 0.003                      |
| <i>t</i> -butylbenzene     | 0.63              | --                 | 0.60                                   | --                         |
| <i>t</i> -butylchloride    | 0.12              | 0.10               | 0.16                                   | 0.22                       |

It is apparent from these data that complexing solvents have very little effect on the contribution of polar structures to the transition state. Only in the case of *t*-butyl chloride is any solvent effect noted. Were the magnitude of this contribution greatly increased, a significant change in the reactivities of, for example, tetramethylsilane and trimethylchlorosilane would have been observed. The situation, however, is not clear cut. Solvent effects in reactions of this type have been previously discussed (31). Opposing effects seem to be operative. The electron affinity of a chlorine atom should be reduced by complexing. A reduction in electron affinity should lead to a smaller contribution from the polar structure II. On the other hand, the reduced reactivity of the chlorine atom will, according to the Hammond principle (29), result in an increased contribution from structures II and III. Since no particular solvent effect has been observed, these two opposing tendencies may be of approximately equal magnitude.

The alternative case was similarly examined. Compounds were compared in which no polar effect is obvious, but whose radicals vary greatly in stability. A marked solvent effect was observed. The solvent was varied from an aliphatic solvent to 4 M benzene to 4 M *t*-butylbenzene to 12 M carbon disulfide. The relative reactivity (tert./prim.) of 2,3-dimethylbutane increased from 4.2 to 20 to 35 to 225. A similar increase was observed in the reactivity ratio (sec./prim.) of the hydrogens of *n*-pentane: 3.7 to 4.9 to 6.8 to 29. Various workers (32,33) have shown that the stabilities of cycloalkyl radicals vary  $C_8 > C_7 > C_5 > C_6$ . In the absence of any added solvent these stability differences are not evident. Photochlorination reactivities are in the sequence  $C_8 : C_7 : C_5 : C_6 :: 1.5 : 1.0 : 1.0 : 1.0$ . In 12 M carbon disulfide the full complement of reactivities is observed;  $C_8 : C_7 : C_5 : C_6 :: 3.8 : 2.0 : 1.2 : 1.0$ . These data indicate that the importance of structure III in the transition state is greatly increased by the presence of a complexing solvent.

Yet a third case may be imagined in which both polar and resonance effects determine reactivities. Since the magnitudes of the polar and resonance effects are interrelated, an increase in the importance of one is concomitant with a decrease in the importance of the other. Such an effect may operate to deemphasize reactivity differences. These differences are illustrated by a comparison of the differences in reactivities evidenced by chloroform and the primary hydrogen atoms of 2,3-dimethylbutane. In the absence of added solvent, chloroform is 200 times less reactive. In better





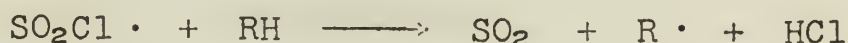
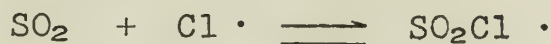


complexing media the relative electron densities become less important and the similar resonance energies of the trichloromethyl and 2,3-dimethylbutyl radicals become apparent. In 4 M t-butylbenzene chloroform is only 60 times less reactive, while in 12 M carbon disulfide the reactivity discrepancy is reduced to 1 to 30. A similar phenomenon is noted in the case of toluene. A primary hydrogen atom of 2,3-dimethylbutane and the methyl hydrogens of toluene are of approximately equal reactivities toward a free chlorine atom. This has been interpreted in terms of a combined resonance and inductive effect (34). However, in 12 M carbon disulfide the methyl hydrogens of toluene are 11 times as reactive as the primary hydrogens of 2,3-dimethylbutane.

In summary, Russell has observed three cases. a) Reactivities are determined mainly by a polar effect and are notably insensitive to the presence of complexing agents. b) Relative reactivities are determined mainly by the resonance energies of the incipient radicals and are very dependent upon the presence of complexing solvents. c) Relative reactivities are dependent upon both polar and resonance effects. It should be noted that cases a) and b) offer a means of qualitative determination of the factors controlling relative reactivities.

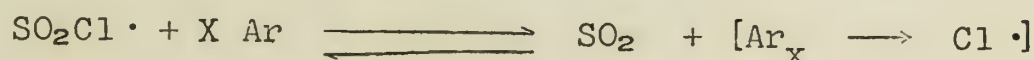
#### SOLVENT EFFECTS IN OTHER SYSTEMS

Chlorinations with sulfuryl chloride have long presented a confusing picture (35). In the photochlorination of 2,2,3-trimethylbutane a relative reactivity (tert./prim.) of 3.2 is noted. Chlorination with sulfuryl chloride leads to a relative reactivity of 7.3 (17). Sulfuryl chloride is similarly selective toward the hydrogens of 2,3-dimethylbutane. A tertiary hydrogen is ten times as reactive as a primary hydrogen when sulfuryl chloride is employed, but only 3.7 times as reactive in the normal chlorination procedure with molecular chlorine. However, the selectivity of sulfuryl chloride is not always evident. It has been observed that p-chlorotoluene is 0.69 times as reactive as toluene with respect to either normal chlorination or sulfuryl chloride (31). Similar results are observed in the case of m-cyanotoluene (31). When an excess of α-d-toluene is chlorinated with either reagent, an isotope effect of 2.1 is noted (31). The enhanced selectivity of chlorination with sulfuryl chloride has been attributed to the formation of a less reactive radical. With molecular chlorine the hydrogen abstraction step involves attack by a free chlorine atom. In the presence of sulfur dioxide, the chlorine atom may be in the form of a sulfuryl chloride radical. Evidence for this intermediate has been



offered (17,36).

In the presence of other complexing agents, e.g., aromatic nuclei, the sulfuryl chloride radical may be replaced by a complex of the type discussed earlier.







The result is that chlorination with either sulfonyl chloride or molecular chlorine in the presence of an aromatic solvent or substrate leads to the same attacking species, the aromatic nucleus-chlorine atom complex. Russell has substantiated this point of view by chlorinating 2,3-dimethylbutane in various aromatic solvents by both the photochlorination and sulfonyl chloride methods (35). The relative reactivities of tertiary to primary hydrogen atoms were compared. In the absence of added solvent, the ratio of the relative reactivities toward sulfonyl chloride to the relative reactivities toward chlorine atoms at 55° was 2.70. As the solvent was varied from 4 M benzene to 4 M *t*-butylbenzene to 8 M benzene, this ratio decreased to 1.91 to 1.32 to 1.12. It is apparent that the reactivity ratios tend to approach unity as the complexing ability of the medium improves. Further substantiation of this concept is offered by an examination of the chlorination of  $\alpha$ -*d*-toluene (35).

The equilibrium constant for complex formation should decrease as the electron affinity of the radical decreases (12). The electron affinities, in kcal./mole, of some radicals common in organic chemistry are (37): chlorine, 88.2; bromine, 81.6; iodine, 74.6; perhydroxyl, 70; hydroxyl, 50; triphenylmethyl, 48; phenoxy, 27; methyl, 25. From these data it may be seen that solvent effects will be more obvious with radicals such as chlorine, bromine and iodine and less apparent with phenoxy and alkyl radicals. Russell (38) has observed solvent effects with *t*-butoxy radicals. They are, as anticipated on the basis of electron affinities, less than those observed with chlorine atoms. Complexes in which the radical donates electrons to the solvent are also conceivable (38), but have not yet been identified.

It has been emphasized that a complexed radical is less reactive than a "free" radical. This decreased reactivity should manifest itself in a rate discrepancy. It is of interest, therefore, that a study of the rate of oxidation of *n*-decanal has been conducted in both *n*-decanal and *n*-decane solution (39). The rate constants for both propagation and termination were found to be 4-5 times faster in *n*-decane solution. This implies a possible complex of aldehyde radicals with aldehyde molecules in the absence of an added solvent. The rates of dissociation of hexaphenylethane in various solvents have been measured (40). Very little change has been noted as the solvent is varied from acetonitrile to carbon disulfide. This is not overly surprising, as a variation in rate would demand solvent participation in the ground or transition states (12). It is significant, however, that the equilibrium constants for the same dissociation vary by a factor of 16 as the solvent is changed through approximately the same range (41).

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# FRIEDEL-CRAFTS SULFONYLATION: MECHANISM AND REVIEW

Reported by R. S. Neale

January 12, 1959

## I. INTRODUCTION

In 1953, Brown and Nelson (1) published the first of several articles dealing with the correlation between the "activity" of the attacking electrophile and its "selectivity", as determined by the relative amounts of o-, m-, and p-isomers formed, in Friedel-Crafts type substitution on aromatic compounds. In time, this correlation became known as the Selectivity Relationship and was expressed (2) by plotting  $\log p_f$  vs.  $\log S_f$ , where  $p_f$  is the partial rate factor for p-substitution in toluene, and

$$S_f = \log \frac{2 \times \% \text{ p-isomer}}{\% \text{ m-isomer}} \cdot \frac{2 \times \% \text{ p-}}{\% \text{ m-}} = \text{P/M ratio.}$$

Using empirical equations (3),  $p_f$  is derived from the relative total rate ratio (T/B) for the reaction in toluene compared to benzene. A straight line relationship is displayed in the case of the majority of electrophilic substitutions considered, with the exception of a few serious discrepancies (1).

The discrepancies, however, were shown to arise from improper use of the literature data, since reinvestigations of selected reactions showed they obey the Selectivity Relationship.

The benzoylation reaction was studied extensively by Brown and his coworkers (2,3,4) who corrected a false point on the Selectivity Relationship which had been plotted from previously reported data. When the benzoylations of benzene and toluene in nitrobenzene were studied using exceptionally pure reagents (3), complex kinetics were found. The reaction with benzene was found to be third order, that with toluene 7/2 order (first order with respect to toluene). Further, the value of  $k_3$  decreased as the amount of aluminum chloride increased, in a non-regular fashion. The value of  $k_{\text{toluene}}/k_{\text{benzene}}$  was found to be that predicted using the Selectivity Relationship. The complexity of the reaction arises from the interaction of aluminum chloride and nitrobenzene. Lebedev (5) has measured the order with respect to aluminum chloride in the benzoylation of benzene using varying mixtures of benzene-nitrobenzene as solvent and has found the estimated order to vary from 0.5 in 100% nitrobenzene to 2.0 in 100% benzene. However, when the reaction is run in bromobenzene, it is cleanly second order (6). Nevertheless, it is obvious that benzoylation is a reaction of low activity and high selectivity.

The kinetics of the Friedel-Crafts sulfonylation of aromatic compounds had been studied extensively in 1914 by Olivier (7,8,9) who usually used either of the two aromatic reactants as solvent and obtained, presumably because of impure materials, second order rate constants that varied markedly with the initial aluminum chloride concentration and, in certain cases, from one run to the next. For example, in the p-bromobenzenesulfonylation of benzene (8) the following data are illustrative.





1.0 mole  $p\text{-BrC}_6\text{H}_4\text{SO}_2\text{Cl}$ 

Solvent: benzene

time min. | %  $p\text{-BrC}_6\text{H}_4\text{SO}_2\text{Cl}$  remaining ( $\text{AgNO}_3$  titration)

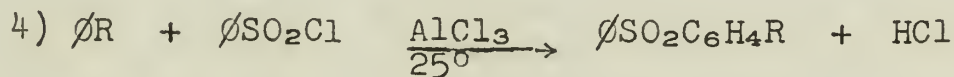
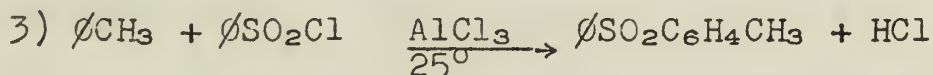
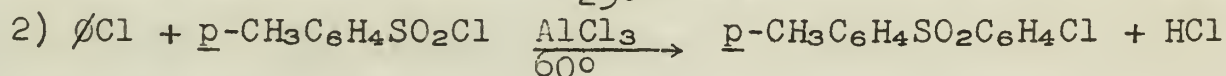
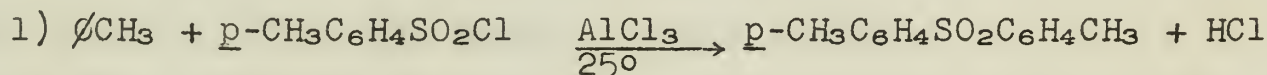
|     | 1.05 mole $\text{AlCl}_3$ | 1.0 mole $\text{AlCl}_3$ | 1.0 mole $\text{AlCl}_3$ |
|-----|---------------------------|--------------------------|--------------------------|
| 0   | 90.6                      | 96.2                     | 92.7                     |
| 30  | 89.5                      | 75.6                     | 89.7                     |
| 60  | 87.2                      | 53.9                     | 83.9                     |
| 180 | 73.3                      | 24.5                     | 44.3                     |

Olivier (9) also obtained data showing the effect on the reaction rate of a para substituent of the sulfonylating species in the reaction with benzene. The ratio  $k_{\text{benzene}}/k_{p\text{-bromobenzeneSO}_2\text{Cl}}$  was 1.9 for the reaction with benzene.

Plotting the sulfonylation reaction point on the Selectivity Relationship seemed unjustified because the data were derived from reactions concerning the two different sulfonylating agents mentioned above. However, it was evident that sulfonylation was a reaction high in activity and low in selectivity, and was therefore different from the closely related benzoylation reaction. Kinetic studies of the sulfonylation reaction were then undertaken by Brown and Jensen in order that the kinetic order, mechanism, and the directive effects in the sulfonylation reaction might be compared with these considerations in electrophilic reactions which obeyed the Selectivity Relationship. In particular, it seemed of interest to determine in what respects the sulfonylation and benzoylation reactions were similar and dissimilar, and whether the sulfonylation reaction obeyed the Selectivity Relationship.

## II. SULFONYLATION IN NITROBENZENE SOLVENT

The reactions studied (10) were the following:



R = H, ethyl, isopropyl, tert-butyl, polymethyl

Data are given in Table I for the reaction between toluene and p-toluenesulfonyl chloride. The reaction was found to be third order, although not cleanly first order with respect to toluene as it was in the case of benzoylation, where the total order was  $7/2$ . That this was not a solvent effect was shown by the addition of cyclohexane to the solution, which lowered the rate 6%. A corresponding increase in the toluene concentration lowered the rate 25%. Hence, the differing polarities of toluene and nitrobenzene were not responsible. It was further found, as in the case of benzoylation, that a decrease in  $\text{AlCl}_3$  concentration produced an irregular increase in the rate. When chlorobenzene (Table II) was substituted for toluene, good third order kinetics were obtained in which the reaction was first order in chlorobenzene and of indefinite order in  $\text{AlCl}_3$ . The addition of excess



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chlorobenzene produced a decrease in  $k_3$  of the order expected for a solvent effect. The nature of the sulfonylating species was found to have no effect upon the reaction except to alter the magnitude of  $k_3$ . The reaction of toluene and benzenesulfonyl chloride at 25° displayed kinetics identical with the reaction involving p-toluenesulfonyl chloride except that

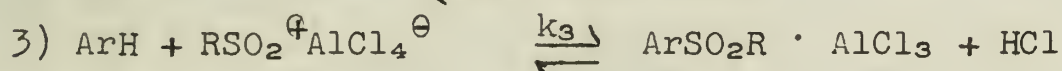
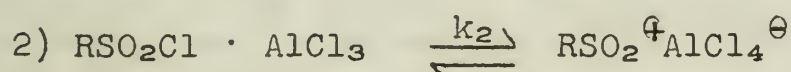
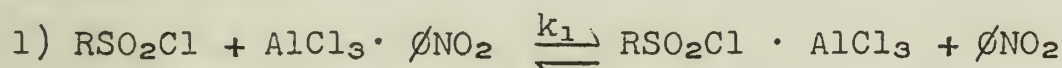
$$k_3 \text{ } \phi\text{SO}_2\text{Cl} = \frac{1}{4} k_3 \text{ } \text{pCH}_3\text{C}_6\text{H}_4\text{SO}_2\text{Cl}.$$

The fourth reaction yielded the following relative rates for equal concentrations of all reactants (0.222 M):

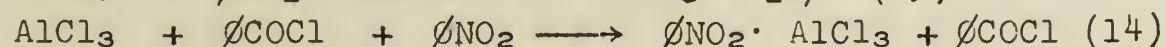
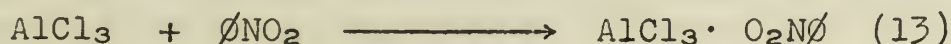
| R             | $k_3$ av. | rel. k |
|---------------|-----------|--------|
| H             | 0.00233   | 1.00   |
| methyl        | 0.0211    | 9.0    |
| ethyl         | 0.0161    | 6.8    |
| i-pr.         | 0.0113    | 4.8    |
| <u>t</u> -bu. | 0.0083    | 3.5    |

This is the order which would be predicted by analogy to benzoylation. Polymethylbenzenes were also studied, and the rate was shown to be about three times that in the toluene reaction and independent of the structure of the polymethylbenzene. That the rate was independent of the initial concentration of polymethylbenzene was shown, for example, by obtaining the same decrease in  $\phi\text{SO}_2\text{Cl}$  concentration with time for three different initial concentrations of mesitylene. The order of the sulfonylation reaction in nitrobenzene therefore became second when a highly reactive aromatic hydrocarbon was used. It is important to note that an unreactive aromatic such as chlorobenzene leads to a third order reaction, while indefinite orders are obtained for the aromatics of intermediate activity, such as toluene.

A mechanism which seems reasonable in describing these rather complex reactions is proposed by Brown (10), who postulates the following three steps:



The mechanism is consistent with both the benzoylation and sulfonylation reactions. However, it does not explain the effect of the initial  $\text{AlCl}_3$  concentration on the rate constant, nor the results of Baddeley (11), who found that acylation of naphthalene occurs at the beta-position in  $\phi\text{NO}_2$  but at the alpha-position in methylene chloride, indicating increased steric bulk in the attacking agent in the former case, presumably a complex involving  $\phi\text{NO}_2$ . However, the significance of these data is partially offset by the fact that the cyclization (12) of 3-( $\alpha$ -naphthyl)-1-propanoyl chloride with  $\text{AlCl}_3$  in  $\phi\text{NO}_2$  occurs mainly in the more activated peri-position, in preference to the beta-position. The assumption that the  $\text{AlCl}_3$  is tied up in a 1:1 complex with nitrobenzene in the presence of a sulfonyl chloride is well supported by Brown who points out the following known reactions and draws the logical conclusion concerning the complex, since  $\phi\text{SO}_3\text{H}$  is a stronger acid than  $\phi\text{COOH}$ .



1. The first part of the report deals with the general situation of the country and the progress of the work during the year. It is divided into two main sections: the first section deals with the general situation and the second section deals with the progress of the work.

2. The second part of the report deals with the results of the work during the year. It is divided into two main sections: the first section deals with the results of the work and the second section deals with the conclusions.

| Table 1 |      |      |
|---------|------|------|
| 1930    | 1931 | 1932 |
| 1000    | 1200 | 1500 |
| 2000    | 2500 | 3000 |
| 3000    | 3500 | 4000 |
| 4000    | 4500 | 5000 |
| 5000    | 5500 | 6000 |

3. The third part of the report deals with the conclusions of the work during the year. It is divided into two main sections: the first section deals with the conclusions and the second section deals with the recommendations.

4. The fourth part of the report deals with the recommendations of the work during the year. It is divided into two main sections: the first section deals with the recommendations and the second section deals with the conclusions.

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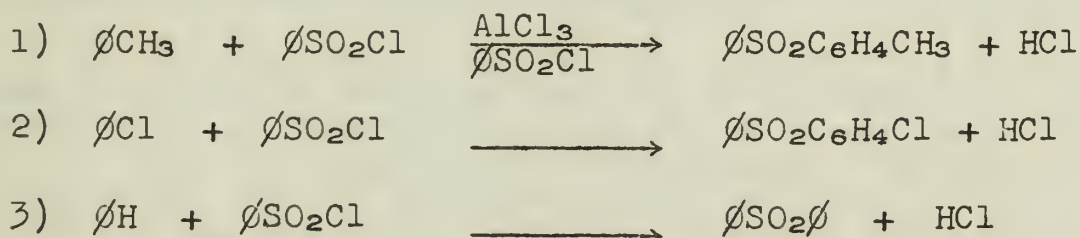
That the actual catalyst is some more complex reaction product of nitrobenzene and  $\text{AlCl}_3$  is suggested by the observed variation in the apparent order of the reaction with respect to  $\text{AlCl}_3$  when nitrobenzene is mixed with other solvents. Lebedev (5) has proposed a partial explanation of his observed 0.5 order in  $\text{AlCl}_3$ -100%  $\phi\text{NO}_2$  in this way.

The T/B ratio for benzenesulfonylation is 9.0. Compared to the ratio (149) found for benzoylation, a quantitative indication of the higher activity of sulfonylation is obtained. An explanation can be advanced on the basis of the relative stabilities of the attacking cation; thus,  $\phi\text{SO}_2^+$  is expected to be less resonance stabilized by multiple bonding to sulfur than is  $\phi\text{CO}^+$  with multiple bonding to carbon. The fact that use of *p*-methylbenzenesulfonyl chloride increases the rate four times over that when benzenesulfonyl chloride is used can be explained by a simple inductive contribution of the *p*-methyl group lending increased stabilization to *p*- $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2^+$  compared to  $\phi\text{SO}_2^+$ , hence favoring step 2 in the proposed mechanism. However, the same inductive effect would make *p*- $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{Cl}$  less acidic than  $\phi\text{SO}_2\text{Cl}$  and thereby favor step 1. A combination of the two possibilities is probably at work.

That the reaction with polymethylbenzenes occurs at a rate which is second order and is independent of the polymethylbenzene would indicate that the rate determining step becomes the ionization step (2) rather than the substitution step (3). It is obvious that the relative rates obtained for reaction with toluene and, for example, mesitylene, cannot be used to determine the relative reactivities of the two compounds. To determine relative reactivities, competition experiments would have to be conducted.

### III. SULFONYLATION IN BENZENESULFONYL CHLORIDE SOLVENT

Because the kinetics of sulfonylation in benzenesulfonyl chloride solvent had been found to follow a second order rate law by Olivier (9) and because the reaction in nitrobenzene was complex, Jensen and Brown (15) restudied the reaction using benzenesulfonyl chloride as the solvent. In this case the reaction was followed by isolating and weighing the sulfone produced. The reactions studied were as follows:

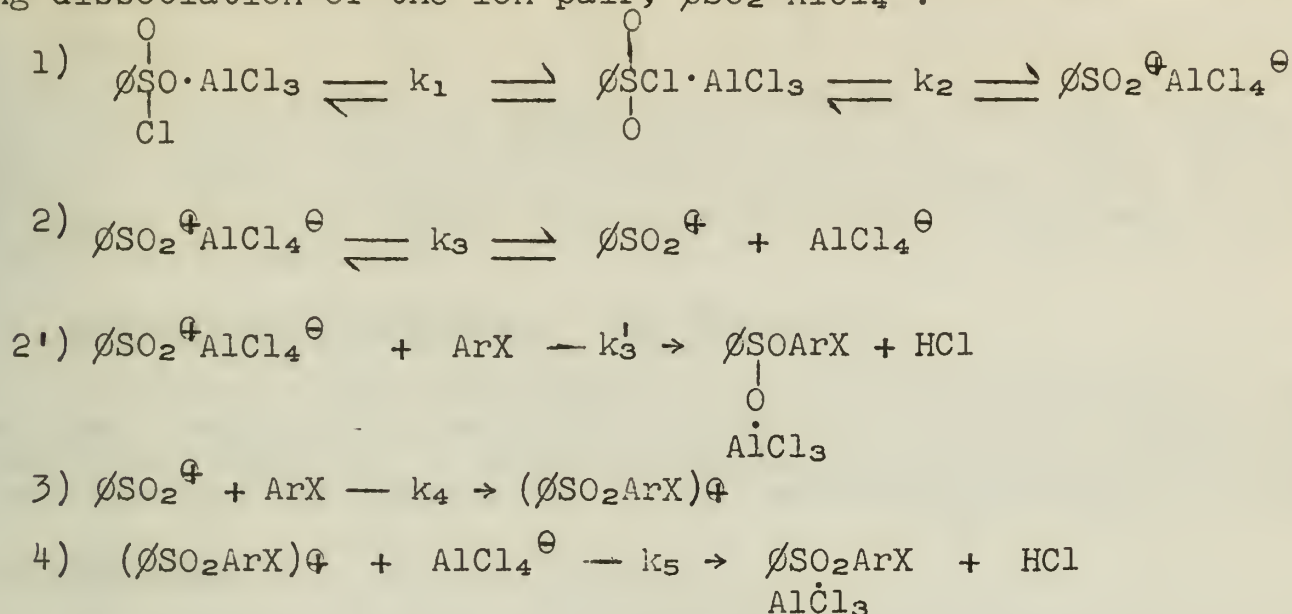


The kinetics of the first reaction were found to follow a definitely second order rate law. The value of  $k_2$  did not drift as the initial  $\text{AlCl}_3$  concentration was varied (see Table IV). The second reaction occurred with a rate of  $3/2$  order. The rate expression is written  $R = k_{3/2} (\phi\text{SO}_2 \cdot \text{AlCl}_3)^{1/2} (\phi\text{CH}_3)$ , since the existence of the 1:1 complex is known (16). Olivier (9) had found the reaction to be second order, but  $k_2$  rose during a run after the reaction was 50% complete. Conversion of Olivier's data to a  $3/2$  order rate constant showed  $k_{3/2}$  to be steady with varied concentrations of chlorobenzene and  $\text{AlCl}_3$ . Constant rates were observed in a given run for the third reaction, but there were obtained varying initial rates as the concentration of the reactants was changed. High concentrations of benzene produced a second order reaction (see the section following on isomer distribution).





The mechanism which best accounts for the difference in kinetic order between reactants of differing activity includes a step involving dissociation of the ion pair,  $\phi\text{SO}_2^+\text{AlCl}_4^-$ .



In the case of toluene, the ion pair is reactive enough to attack before ionization occurs (step 2), leading to a second order reaction involving steps 1 and 2'. In the case of chlorobenzene the attacking agent is the more reactive  $\phi\text{SO}_2^+$ . That the reaction is 3/2 order can be shown by solving for  $(\phi\text{SO}_2^+)$  in the rate equation  $R = k(\phi\text{Cl})(\phi\text{SO}_2^+)$ , using the equilibrium in step 2 above. Since benzene is an aromatic of intermediate activity, it is not unreasonable to suppose that the reaction occurs by both paths and that a high concentration of benzene would favor step 2' leading to the observed second order kinetics, because the dissociated ion,  $\phi\text{SO}_2^+$ , is used up at a rate exceeding that of its formation. The assumption is made that  $k_3$  is of the same order of magnitude as  $k_3'$ . The addition of more  $\text{AlCl}_3$  further increases the concentration of the ion pair relative to the dissociated ions. The net result is the minimizing of the 3/2 order reaction with benzene which then reacts, for the most part, directly with the ion pair.

#### IV. ISOMER DISTRIBUTION IN BENZENESULFONYLATION REACTIONS

The logical conclusion to the studies of Jensen and Brown on the previously cited material was the investigation of the isomer distribution (17) in sulfonylation reactions to determine whether these reactions obey the Selectivity Relationship. The data derived from the experiments run in benzenesulfonyl chloride solvent were employed to calculate the T/B ratio. For the reaction with benzene,  $k_2 = 0.0118$  l/mol. min. For the reaction with toluene,  $k_2 = 0.095$  l/mol. min. The T/B ratio was found to be  $8.0 \pm 1.0$ , which is about the same as found for the benzenesulfonylation reaction in nitrobenzene. The isomer distribution was estimated by infrared analysis of the sulfones. Pure samples of each isomer were prepared from benzene and the appropriate toluenesulfonyl chlorides and synthetic mixtures were analyzed to standardize the method. The percents of tolyl phenyl sulfone obtained were 28.4% ortho-, 8.7% meta-, and 62.9% para-. From the relative rates, the T/B ratio, and the isomer distribution, partial rate factors were calculated which agreed with those obtained (18) using the Selectivity Relationship, assuming it to be valid for this reaction. For the relation of sulfonylation to other electrophilic reactions, the reader should consult the original paper (2).





|          | $c_f$ | $m_f$ | $p_f$ | T/B           |
|----------|-------|-------|-------|---------------|
| Observed | 6.8   | 2.1   | 30.2  | 8.0 $\pm$ 1.0 |
| Calc'd.  | 7.3   | 2.3   | 33.0  | 8.7           |

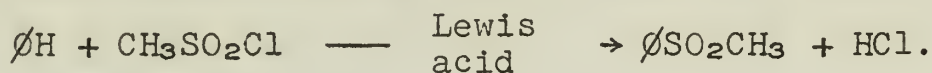
The large amount of ortho-isomer (28.4%) obtained, compared with the 9.3% ortho- found in benzoylation reactions, is explained by concluding that for reactants of about the same steric bulk, the species of higher activity ( $\phi\text{SO}_2^+$ ) has a smaller steric requirement than that ( $\phi\text{CO}^+$ ) of low activity.

#### V. SULFONYLATION-SYNTHESSES - SEE TABLE III.

A review of the sulfonylation reaction has been made by Suter (19), who has tabulated the reactions reported up to 1943. Further work is listed in Table III. A brief discussion of the reported cyclization reactions and the preparation of the sulfonylating agents follows.

#### Cyclizations.

The internal condensation of  $\omega$ -phenylalkanesulfonyl chlorides has been shown (20) to yield 5-, 6- and 7-membered rings but not 4- or 8-membered rings. The position attacked is always that ortho- to the side chain. It was further found that the reaction is very sensitive to the nature and amount of the Lewis acid catalyst, since  $\text{SnCl}_2$  in sym-tetrachloroethane failed to promote the reaction and use of  $\text{AlCl}_3$  in the same solvent led to tars. Use of  $\text{AlCl}_3$  (1.1 to 1.5 equivalents) in nitrobenzene at temperatures ranging from 7 to  $100^\circ$  gave products as indicated in Table III. Later data (21) permit comparisons to be made between other Lewis acids, as shown below, for the reaction

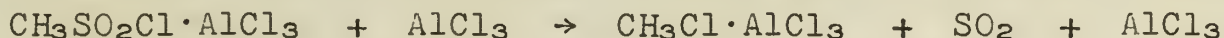


| Lewis Acid<br>1 mole | Rx. time to<br>steady [sulfone] | % conversion |
|----------------------|---------------------------------|--------------|
| $\text{AlCl}_3$      | 8 hr.                           | 75           |
| $\text{FeCl}_3$      | 15                              | 70           |
| $\text{SbCl}_5$      | 12                              | 30           |
| $\text{AlBr}_3$      | tar                             | --           |
| * $\text{BF}_3$      | (28)                            | 0            |

\*Equivalent amount not soluble in Rx. mixture (0.5 eq. sol.).

| Lewis Acid      | Equivalents | % conversion |
|-----------------|-------------|--------------|
| $\text{FeCl}_3$ | 0.8         | 70           |
|                 | 1.0         | 70           |
|                 | 1.2         | 70           |
| $\text{AlCl}_3$ | 0.8         | 60           |
|                 | 1.0         | 75           |
|                 | 1.2         | 40           |

It is evident that use of an excess of  $\text{AlCl}_3$  may lead to decreased yields with aliphatic sulfonyl chlorides, possibly according to the equation below. The odor of  $\text{SO}_2$  is easily detectable (21). However,







excess  $\text{AlCl}_3$  has no effect on the yield in reactions involving aromatic sulfonyl chlorides (19).

It would seem best to employ an excess of the aromatic substrate as solvent if possible. Various solvents employed (21) in the methanesulfonylation of benzene led either to decreased yields or to increased reaction times. The solvents employed were those listed below.

|  |   |
|--|---|
| $\text{CS}_2$                                  | $\text{AlCl}_3 \cdot \text{RSO}_2\text{Cl}$ complex insoluble |
| pet. ether                                     | "   |
| $\text{Cl}_2\text{C}=\text{CCl}_2$             | Low temp. req'd. to avoid Rx. with $\text{AlCl}_3$ .          |
| $\text{Cl}_2\text{CHCHCl}_2$                   | "   |
| $\text{O}_2\text{N}$                           | Hard to remove if sulfone distills with steam                 |
| $\text{CH}_3\text{CH}_2\text{CH}_2\text{NO}_2$ | Leads to decomp. or increased Rx. times                       |

Condensations of  $\omega$ -( $\alpha$ -naphthyl)-alkanesulfonyl chlorides (22) with  $\text{AlCl}_3$ - $\text{O}_2\text{N}$  led to an interesting observation. Ring closure always occurred in the beta-position and no peri-isomer was ever detected. For the case of 2-( $\alpha$ -naphthyl)-1-ethanesulfonyl chloride this is especially surprising since the analogous acyl chloride closes in  $\text{AlCl}_3$ -ligroin or HF to yield the peri-isomer nearly exclusively (12) and since cyclization in the benzene series gives a much higher yield of 6- than 5-membered cyclic sulfone (20). However, since Baddeley (11) found that acylation of naphthalene in  $\text{O}_2\text{N}$  occurred in the beta-position, it is not unreasonable to suppose that the peri-position is sterically unfavored for cyclization; the  $\text{RSO}_2\text{Cl} \cdot \text{AlCl}_3$  complex is probably solvated by  $\text{O}_2\text{N}$ .

### The Sulfonylating Agent

Benzenesulfonic anhydride has been little used (23) but is considered superior to the corresponding acid chloride by Field (24) who prepared the anhydride by the action of  $\text{P}_2\text{O}_5$  on the sulfonic acid. An inert solid support was used to facilitate extraction of the product with ethylene chloride from the gummy reaction mixture.

There seem to be two standard methods of preparing the more commonly used sulfonyl chlorides. The first (20,25) involves treatment of the alkyl bromide with  $\text{Na}_2\text{S}_2\text{O}_3$ , then addition to the alkylthiosulfate solution of  $\text{I}_2$  and oxidation (26) with chlorine gas of the resulting disulfide (96% in the case of bis-(3- $\beta$ -1-propyl) disulfide) to the sulfonyl chloride (69% in the case of 3- $\beta$ -1-propanesulfonyl chloride). The reaction with  $\text{I}_2$  is complex but it is probable that the mercaptan is not involved (25).

The second method (20,22) is also carried out starting with the alkyl bromide; the bromide is heated under reflux with a solution of  $\text{Na}_2\text{SO}_3$  to form the sodium sulfonate and the crude salt is treated with  $\text{PCl}_5$  to give the sulfonyl chloride in 50-55% yield. It is interesting to note that  $\alpha$ -naphthylmethanesulfonyl chloride (22) could not be made in this way. It is suggested that the sulfonyl chloride initially formed loses chloride under the influence of  $\text{PCl}_5$  to give the non-stabilized sulfonyl cation which then loses  $\text{SO}_2$  to give the resonance-stabilized carbonium ion. The reaction product is  $\alpha$ -chloromethylnaphthalene.

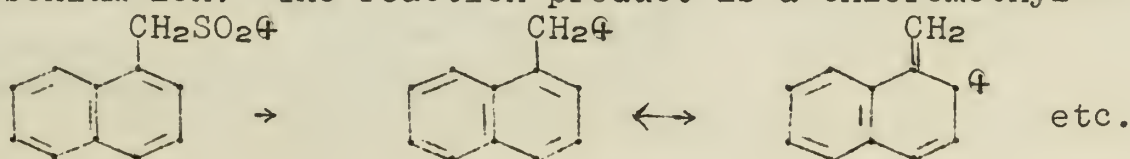






TABLE I

Reaction of toluene, *p*-toluenesulfonyl chloride,  $\text{AlCl}_3$ ,  $\text{O}_2\text{NO}$   
 $25^\circ$   
 Conc. moles/liter

| $[\text{OCH}_3]$ | $[\text{p-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{Cl}]$ | $[\text{AlCl}_3]$ | $k_3 \text{ l}^2/\text{mol}^2 \text{ min.}$ |
|------------------|---|-------------------|---|
| 0.317            | 0.157   | 0.317             | 0.0735                                      |
| 0.317            | 0.317   | 0.317             | 0.00794                                     |
| 0.317            | 0.473   | 0.317             | 0.0765                                      |
| 0.317            | 0.317   | 0.0793            | 0.13  |
| 0.317            | 0.317   | 0.171             | 0.0955                                      |
| 0.317            | 0.317   | 0.525             | 0.0595                                      |
| 1.215            | 0.317   | 0.317             | 0.0291                                      |
| 0.520            | 0.317   | 0.317             | 0.0598                                      |
| *0.317           | 0.317   | 0.317             | 0.0745                                      |

\* 0.189 M cyclohexane added.

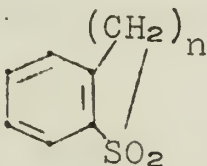
TABLE II

Reaction of chlorobenzene, *p*-toluenesulfonyl chloride,  $\text{AlCl}_3$   
 $\text{O}_2\text{NO} - 60^\circ - \text{conc. m/l.}$

| $[\text{OCl}]$ | $[\text{p-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{Cl}]$ | $[\text{AlCl}_3]$ | $k_3 \text{ l}^2/\text{mol}^2 \text{ min.}$ |
|----------------|---|-------------------|---|
| 0.305          | 0.305   | 0.119             | 0.269                                       |
| 0.305          | 0.305   | 0.305             | 0.121                                       |
| 0.305          | 0.305   | 0.805             | 0.00565                                     |
| 0.117          | 0.305   | 0.305             | 0.134                                       |
| 0.831          | 0.305   | 0.305             | 0.108                                       |
| 0.305          | 0.118   | 0.305             | 0.123                                       |
| 0.305          | 0.821   | 0.305             | 0.108                                       |

TABLE III

Friedel-Crafts Sulfonylation Reactions Since 1944.

| Substrate   | Sulfonylating Agent  | Product   | Yield %                     | Ref. | Notes  |
|---|--|---|-----------------------------|------|--|
| $\text{O}(\text{CH}_2)_n\text{SO}_2\text{Cl}$<br>n = 1<br>2<br>3<br>4<br>5  | cyclization  |                                      | 0<br>36<br>62-76<br>30<br>0 | 20   | $\text{AlCl}_3$ in $\text{O}_2\text{NO}$<br>$7^\circ$ and $25^\circ$ , 300<br>and 30 min.<br>$80^\circ - 60 \text{ min.}$<br>$90^\circ - 150 \text{ min.}$<br>$90^\circ - 75 \text{ min.}$<br>$90^\circ$ and $60^\circ -$<br>60 and 120 min. |
| $\text{OH}$   | $\text{CH}_3\text{SO}_2\text{Cl}$  | $\text{OSO}_2\text{CH}_3$   | Poor                        | 27   | XS $\text{AlCl}_3$   |
| $\text{OCH}_3$  | $\text{OCH}_2\text{SO}_2\text{Cl}$   | Tars  |                             | 28   | $\text{AlCl}_3$  |
| $\text{p-CH}_3\text{OC}_6\text{H}_4\text{OCH}_3$<br>$(\text{CH}_3)_2\text{CH}(\text{CH}_2)_2\text{SO}_2\text{Cl}$ | $\text{CH}_3\text{SO}_2\text{Cl}$<br>$(\text{CH}_3)_2\text{CH}(\text{CH}_2)_2\text{SO}_2\text{Cl}$ | $\text{p-CH}_3\text{OC}_6\text{H}_4\text{OSO}_2\text{CH}_3$<br>$\text{p-CH}_3\text{OC}_6\text{H}_4\text{OSO}_2\text{R}$ |                             | 29   | $\text{ZnCl}_2$  |



| Date   | Description | Amount | Balance |
|--------|-------------|--------|---------|
| Jan 1  | To Balance  | 100.00 | 100.00  |
| Jan 5  | By Cash     | 25.00  | 125.00  |
| Jan 10 | To Cash     | 15.00  | 110.00  |

1914-1915

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| Date   | Description | Amount | Balance |
|--------|-------------|--------|---------|
| Jan 15 | To Cash     | 10.00  | 100.00  |
| Jan 20 | By Cash     | 5.00   | 95.00   |
| Jan 25 | To Cash     | 10.00  | 85.00   |

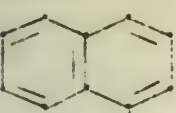
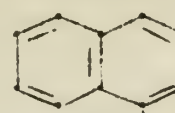
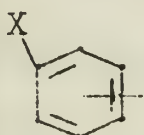
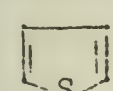
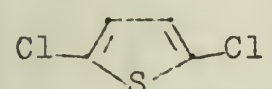
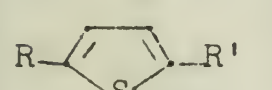
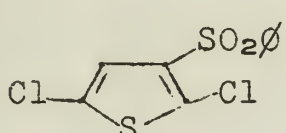
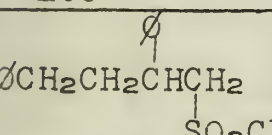
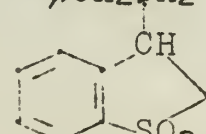


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| Date   | Description | Amount | Balance |
|--------|-------------|--------|---------|
| Jan 30 | To Cash     | 10.00  | 75.00   |

| Substrate   | Sulfonylating Agent  | Product  | Yield %                           | Ref. | Notes  |
|---|--|--|-----------------------------------|------|--|
| <br>$(\text{CH}_2)_n\text{SO}_2\text{Cl}$<br>$n = 2$<br>$3$<br>$4$  | cyclization  | <br>$(\text{CH}_2)_n\text{SO}_2$                                | 54<br>65<br>16                    | 22   | $\text{AlCl}_3$ - $\text{NO}_2$<br>$25^\circ$ - 2 hr.,<br>then $70^\circ$ -2 hr.   |
| $\phi\text{H}$<br>$\phi\text{CH}_3$<br>$\phi\text{Cl}$<br>$\phi\text{Br}$<br>$\phi\text{F}$<br>$\phi\text{OMe}$   | $\text{CH}_3\text{SO}_2\text{Cl}$<br>" "<br>" "<br>" "<br>" "<br>" " | $\phi\text{SO}_2\text{CH}_3$<br><br>$\phi\text{OSO}_2\text{Me}$ | 76.8<br>52<br>72<br>56<br>73<br>- | 21   | 1 eq. $\text{AlCl}_3$ /<br>1 eq. $\text{CH}_3\text{SO}_2\text{Cl}$<br>15% <u>meta</u> , 36%<br><u>para</u><br>60% <u>para</u> after<br>ReX<br><u>para</u><br><u>para</u>   |
| <br><br><br>$\text{R}=\text{R}'=\text{H}, \text{CH}_3, \text{I}$<br>$\text{R}=\text{I}, \text{R}'=\text{Cl}$ | $\phi\text{SO}_2\text{OSO}_2\phi$<br>$\phi\text{SO}_2\text{Cl}$<br>" | tars<br><br>tars   | 24                                | 23   | Benzenesulfon-<br>ic anhydride,<br>$\text{AlCl}_3$ or $\text{H}_3\text{PO}_4$<br><br>$\text{AlCl}_3, \text{CS}_2$ , 47<br>hr., room temp.<br><br>Cat. used were<br>$\text{AlCl}_3$ , $\text{FeCl}_3$ ,<br>$\text{SnCl}_2$ , $\text{I}_2$ |
| $\phi\text{R}; \text{R} = \text{H}$<br>$\text{Br}$<br>$(\text{EtO}_2\text{C})_2\text{CH}^\ominus$<br>$\text{EtO}^\ominus \text{Mg}^{++}$  | $\phi\text{SO}_2\text{OSO}_2\phi$<br>" "<br>"                        | $\phi\text{SO}_2\phi$<br>$\phi\text{SO}_2\text{C}_6\text{H}_4\text{Br}$<br><br>$\phi\text{SO}_2\text{CH}(\text{CO}_2\text{Et})_2$                | 93<br>74<br>(para)<br><br>53      | 24   | 99% crude<br>91% crude<br><br>Before ReX   |
| <br>$\phi\text{CH}_2\text{CH}_2\text{CH}(\text{SO}_2\text{Cl})\text{CH}_2$  | cyclization  | <br>$\phi\text{CH}_2\text{CH}_2$                              |                                   | 30   | $\text{AlCl}_3$  |
|   | $\phi\text{SO}_2\text{Cl}$   | <br>$\text{SO}_2\phi$   | 90                                | 31   | $\text{SnCl}_2$ , $140^\circ$ ,<br>10 min.   |
| $p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{Cl}$   |  | $\alpha\text{-ArSO}_2\text{C}_6\text{H}_4\text{CH}_3$  | 88                                |      | "  |

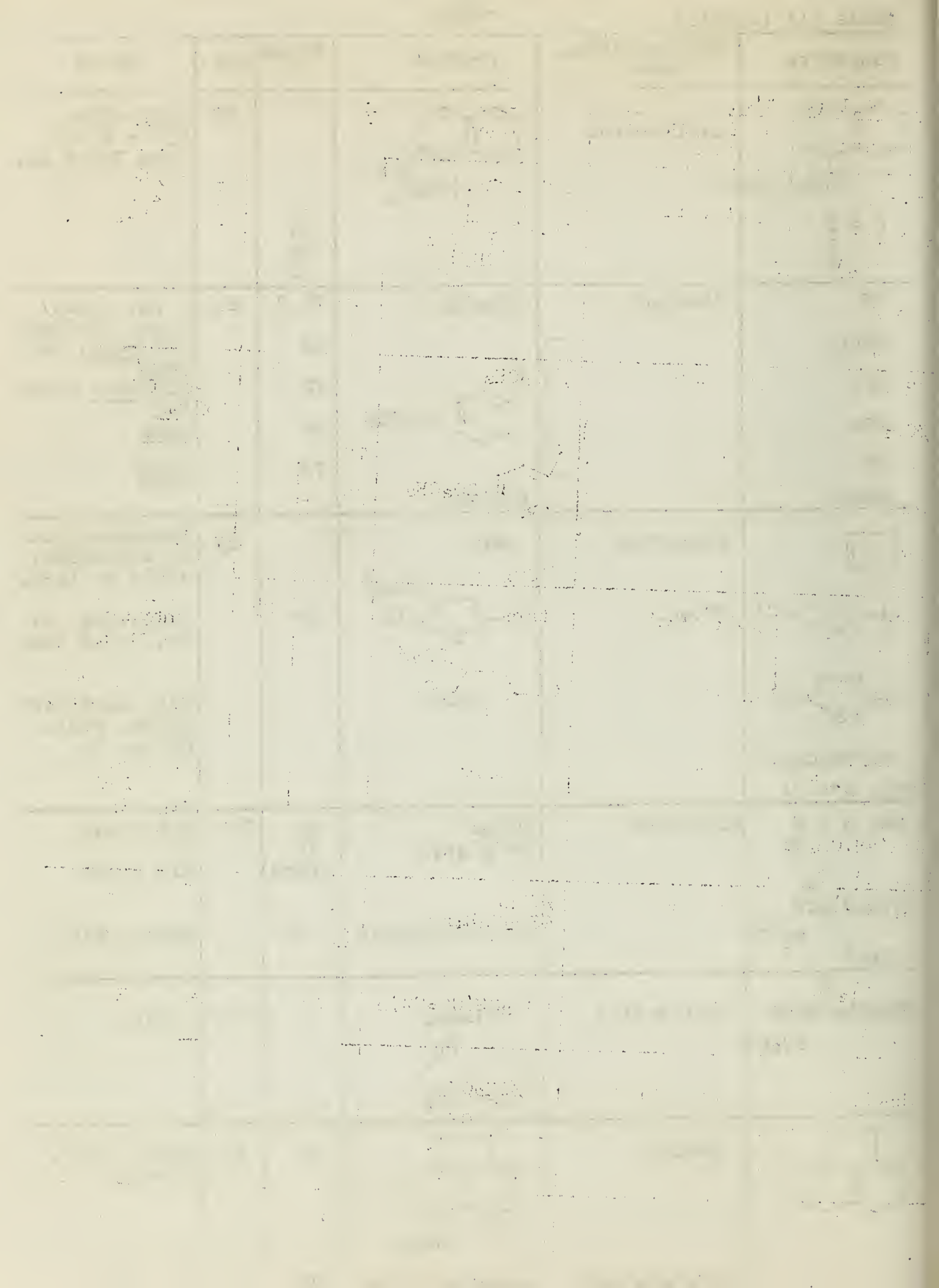
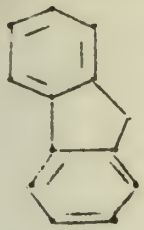
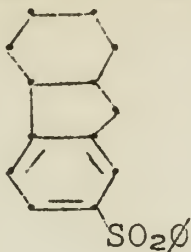




Table III (cont'd)

| Substrate  | Sulfonylating Agent                                     | Product   | Yield % | Ref. | Notes  |
|--|---|---|---------|------|--|
|  | $\phi\text{SO}_2\text{Cl}$                              |  | 92      | 31   | Product checked by synthesis from other $\text{ArSO}_2\text{Cl}$ |
|  | $p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{Cl}$ | $\text{ArSO}_2\text{C}_6\text{H}_4\text{CH}_3$                                    | 94      |      |  |

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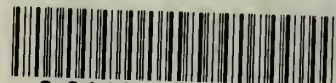








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